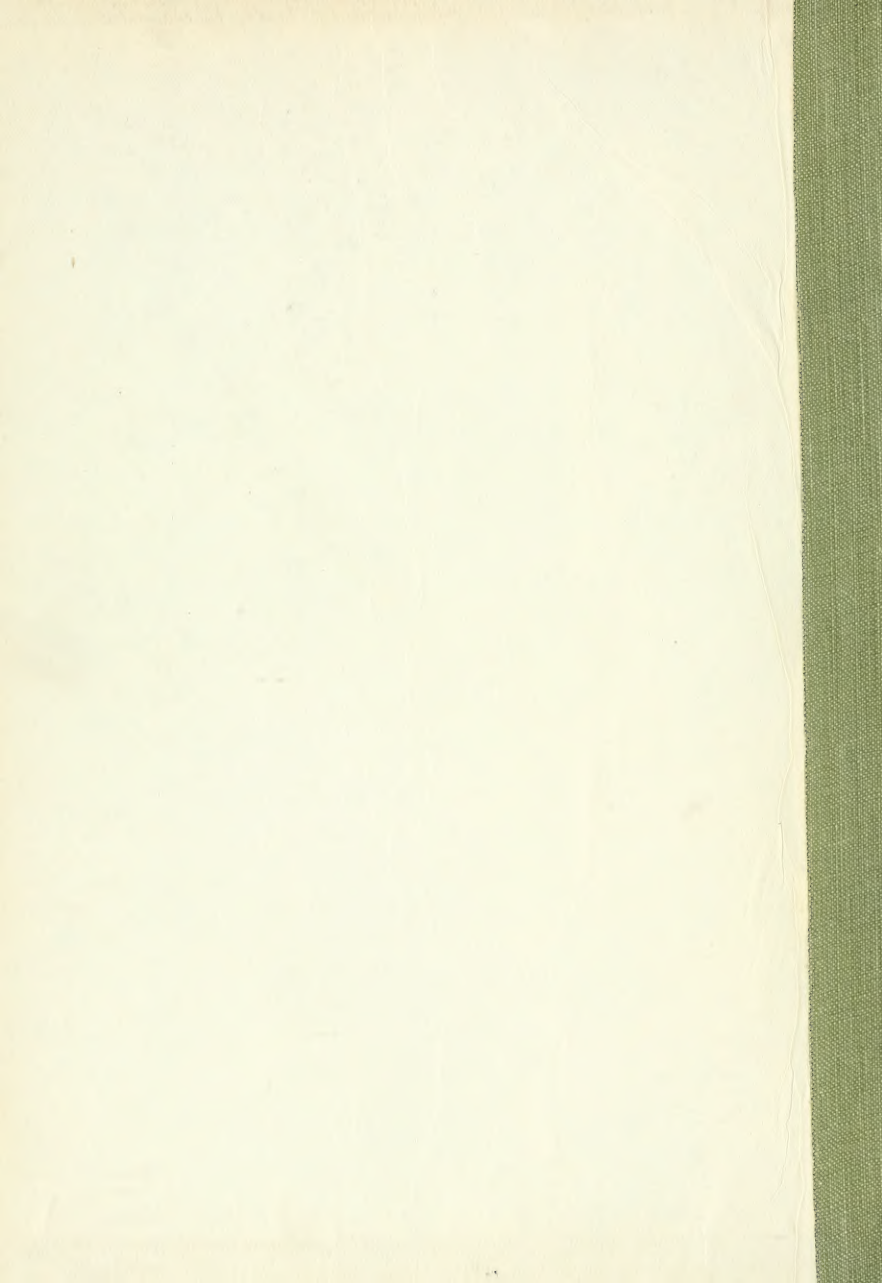


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THE CAUSE OF INCREASED VASCULAR SOUNDS AFTER EPINEPHRIN INJECTIONS.

By JOHN K. LEWIS and A. W. HEWLETT.

(From the Department of Medicine, Stanford Medical School.)

It is well known that certain individuals show a definite reaction after the subcutaneous or intramuscular injection of epinephrin.^{2,5,6} There is increased pulse pressure, increased pulse rate, tremor, palpitation and apprehensive sensations. In addition, the arterial pulse in the arm becomes larger and shows a more pointed form,⁴ and the vascular sounds heard during the auscultatory determinations of blood pressure become louder.^{1,4} The cause of the increase in vascular sounds is not known. Presumably it could be due either to changes in the systolic output from the heart or to local changes in the arteries of the arm. In the present study an attempt was made to throw light on this question.

Changes in the vascular sounds following epinephrin injections were correlated with changes in the pulse pressure, in the size of the volume pulse and in the pulse form. The increase in pulse pressure, produced by epinephrin, is presumably due to an increased systolic output from the heart. The more pointed pulse form, in the presence of an increased systolic output, is presumably due to relaxation of the larger arm arteries. The increased size of the volume pulse may be attributed to either or both of these factors. Thus we see that by correlating changes in the loudness of the vascular sounds with changes in the pulse pressure and pulse form, one might obtain some indication of the cause of the louder vascular sounds commonly heard after injecting epinephrin.

Twelve individuals were tested. Blood pressure, pulse rate, tremor, etc., were observed as in the cases tested for epinephrin hypersensitiveness by Goetch.² In addition, the intensity of the vascular sounds was noted and tracings were made which showed the size and form of the volume pulse waves.

The individuals tested were all males from the medical clinic wards of Lane Hospital. Most of them had entered the hospital for diagnosis. Patients were selected who on account of nervousness or vascular instability seemed likely to react to the drug. All tests were conducted with the patient lying down. The blood pressure was taken with a mercury manometer,

the vascular sounds being observed by placing a small bell stethoscope over the artery just distal to the cuff. The raised intensity of the sounds was estimated and recorded with plus signs, care being taken to eliminate, so far as possible, variations due to changes in position and pressure of the stethoscope. Records of the volume pulse in the arm were taken with an air plethysmograph and a Frank capsule, a method²³ which made it possible to measure approximately the size of the pulse waves.

While the patient lay quiet tracings of the volume pulse, and records of blood pressure, pulse rate and intensity of the vascular sounds were made. After the blood pressure and pulse rate had become constant, from 0.5 c.c. to 1.0 c.c. of a 1:1,000 solution of epinephrin was injected deep into the muscles just below the clavicle, the dose being varied somewhat according to the probability of obtaining a reaction.

Observations were continued until the reaction from the drug subsided. The various observations were made in rapid succession, pulse rate and blood pressure readings being taken one or two minutes after each volume pulse tracing. The cycle of records were repeated on an average every four minutes during the height of the reaction.

Of the twelve patients to whom epinephrin was given, three showed no reaction, two showed atypical reactions, and seven gave definite reactions. In typical reactions there was an increase in systolic pressure, pulse pressure and pulse rate. The diastolic pressure usually remained constant or fell, the latter being the more common. During the reaction patients frequently become apprehensive and nervous and usually developed tremors. A summary of the nine reactions is given in Table I.

With one exception, *Case 4*, all the patients who reacted at all to the drug showed a definite increase in vascular sounds. These became louder and more snapping in quality, making it easy to obtain blood pressure readings. This alteration in sounds was present during all phases of the auscultatory determination of blood pressure, but was most marked in the third phase. In the one instance, where an increased intensity of the vascular sounds was not recorded (*Case 4*), the sounds became more clear and snapping. There was usually an increase in the pulse volume; although in some cases this was so slight that it might be attributed to a technical error. Every case showed some increase in the pointed quality of the pulse wave.

In most cases the change in vascular sounds was accompanied by changes in pulse pressure, pulse form and pulse size, the cases which showed the greatest increase in vascular sounds also showing the greatest increase in these other factors (Table I). This relationship was most exact with regard to the pulse pressure. In most reactions the sounds were observed to be louder as long as the pulse pressure increase lasted. This was true whether the diastolic pressure rose, fell, or remained constant. In one instance, *Case 2*, with an atypical reaction, no definite relationship between pulse pressure and vascular sounds was observed. In the second recorded observation on this patient the sounds had increased while the pulse pressure

TABLE I.

Effect of epinephrin on blood pressure, vascular sounds and pulse waves.

Case.	Dose in cc.	Time after inject.	Blood pressure.			Vascular sounds.	Pulse.		Pulse rate.
			Syst.	Diast.	Pulse.		Pointed quality.	Volume of pulse.	
1	0.8	Before	122	82	40	+	±	0.79	84
		1 min.	122	82	40	+	++	1.07	92
		6 "	144	66	78	++	++	1.17	90
		66 "	142	74	68	+±	++	0.92	96
		81 "	130	76	54	+	+	0.90	90
2	0.5	Before	134	94	40	±	—	0.35	70
		3 min.	118	80	38	+	±	0.31	96
		10 "	136	84	52	+	+	0.41	84
		61 "	130	92	38	±	+	0.44	90
3	1.0	Before	118	84	34	±	—	0.52	66
		13 min.	118	82	36	±	—	0.65	70
		29 "	126	80	46	+	+	0.72	78
		55 "	122	80	42	+	±	0.57	78
		67 "	118	82	36	±	±	0.56	76
4	0.8	Before	110	78	32	Muffled	+	0.48	58
		4 min.	140	80	60	Snapping	+	0.57	72
		27 "	134	74	60	Snapping	++	0.63	68
		52 "	122	82	40	Booming	+	0.63	62
5	1.0	Before	118	84	34	+	±	0.94	54
		10 min.	160	92	68	++	+	1.10	66
		14 "	140	88	52	+	+	1.14	68
		30 "	128	82	46	+	++	1.16	68
6	0.5	Before	112	74	38	+	+	0.93	68
		4 min.	146	66	80	+±±	++	1.16	80
		11 "	132	66	66	++	++	1.26	80
		39 "	126	74	52	++	+±	1.15	74
		55 "	122	80	42	+	+	1.16	80
7	0.5	Before	110	74	36	+	±	0.98	58
		4 min.	112	74	38	+	?	1.23	64
		15 "	124	66	58	+±	+±	1.29	66
		40 "	122	68	54	+±	+	1.17	64
8	0.5	Before	110	68	42	+	+	0.77	68
		7 min.	116	60	56	+±	++	0.88	80
		24 "	130	68	62	+±	++	0.86	86
		33 "	126	70	56	+±	+±	0.88	86
9	0.8	Before	110	78	32	±	±	0.49	72
		10 min.	128	70	58	+±	+	0.60	74
		23 "	126	70	56	+±	+	0.63	80
		30 "	122	70	52	+±	+	0.53	80

remained constant and the systolic and diastolic pressure fell. Later the pressures increased with no further change in sounds. In *Case 4* the increased pulse pressure was accompanied by a change in the quality but not in the loudness of the sounds.

The pulse form and pulse volume also varied with the changes in vascular sounds, but the relationship was not a close one. In two instances, *Cases* 1 and 7, a definite increase in volume pulse and pointed quality of pulse wave occurred before the vascular sounds had increased (Fig. 1). In other instances, *Cases* 2 and 5, the change in pulse form and size persisted after the sounds had diminished. In *Cases* 6 and 7, although the pointed quality of the pulse wave diminished with the vascular sounds, the increase in volume pulse persisted. Thus we see that the increase in the loudness of the vascular sounds following an injection of epinephrin was more closely related to the increase of pulse pressure than to either the increased size or to the pointed form of the volume pulse.

Nitroglycerine has been shown to cause a conspicuous increase in the size and pointed quality of the volume pulse in the arm.² In order to compare the effects of this drug with those of epinephrin, two experiments were made. In one, 0.01 gr. of nitroglycerine was placed under the tongue during a reaction to epinephrin and in the other a similar amount was given alone. A summary of the results of these experiments is given in Table II.

TABLE II.

Effect of nitroglycerine administered under the tongue. Case 9, epinephrin and nitroglycerine ; Case 10, after nitroglycerine alone.

Case.	Dose, gr.	Time after admin.	Blood pressure.			Vascular sounds.	Pulse.		Pulse rate.
			Syst.	Diast.	Pulse.		Pointed quality.	Volume of pulse.	
9	0.01	Before*	122	70	52	+ ±	+	c.c. 0.53	80
		6 min.	108	80	28	±	+++	1.01	92
		19 "	108	80	28	±	++	0.80	84
		24 "	110	78	32		++	0.72	76
10	0.01	Before	104	80	24			0.51	78
		14 min.	96	80	16	±		0.83	70

* Before nitroglycerine and 30 minutes after epinephrin.

Pulse tracings of the first experiment are shown in Fig. 2. In the instance in which the nitroglycerine was given, during a reaction to epinephrin (*Case* 9), there was a prompt decrease in vascular sounds and pulse pressure and an increase in the size and pointedness of the pulse over that which had already been caused by epinephrin. In the experiment in which nitroglycerine alone was given (*Case* 10) there was a drop in systolic, diastolic and pulse pressure, along with much increase in the volume of the pulse and in its pointed quality, the vascular sounds remaining unchanged.

The action of tyramin on the circulation in the arm may be mentioned here for comparison with the action of epinephrin and nitroglycerine. Hewlett¹ found that intramuscular injections usually caused an increase in pulse pressure, an increase in pulse volume and a less pointed form of pulse wave. These were accompanied by an increase in the vascular sounds.

Table III summarises the usual effect of these three drugs upon the vascular sounds, the pulse pressure and the volume pulse in the arm. It shows that, so far as these drug effects are concerned, an increase in the loudness of the vascular sounds is associated with an increase in pulse pressure rather than with changes in the form or size of the volume pulse in the arm. Nitroglycerine, which causes no increase in loudness, likewise

TABLE III.
Effects of epinephrin, nitroglycerine and tyramin.

Drug.	Vascular sounds.	Pulse pressure.	Pulse size.	Pulse form.
Epinephrin	Increased	Increased	Increased	More pointed.
Nitroglycerine	Unchanged	Unchanged or diminished	Increased	More pointed
Tyramin	Increased	Increased	Increased	Less pointed

causes no increase in pulse pressure; while tyramin and epinephrin cause an increase in both the pulse pressure and the loudness of the sounds. An increased volume of the pulse is accompanied either by no increase in sounds (nitroglycerine) or by an increase (tyramin and epinephrin). Finally, a more pointed pulse form is accompanied either by no increase in the loudness (nitroglycerine) or by an increase (epinephrin): while a less pointed pulse may be accompanied by louder sounds (tyramin).

CONCLUSIONS.

1. A typical epinephrin reaction is accompanied by an increase in the loudness of the sounds heard during the auscultatory determination of blood pressure.

2. The correlation of the changes in sounds with the changes in pulse pressure, while not perfect, is better than the correlation between the changes in sounds and the changes in the volume pulse.

3. A comparison of the effects produced by epinephrin, nitroglycerine and tyramin likewise shows that the correlation of changes in vascular sounds with changes in pulse pressure is more exact than the correlation with changes in pulse form or pulse volume.

4. It is inferred that these drugs influence the vascular sounds more through their effect on the systolic output from the heart than through their effect on the blood vessels.

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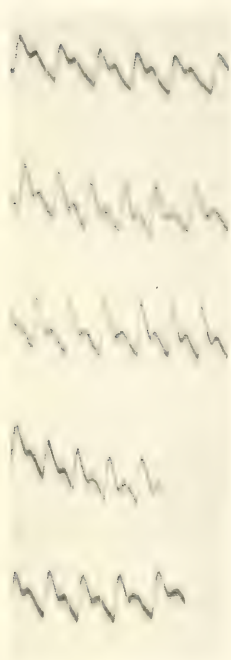


FIG. 1.

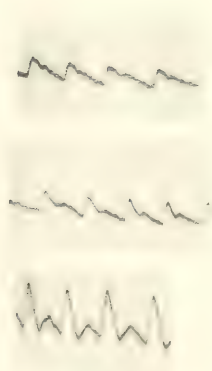


FIG. 2.

Fig. 1. Pulse tracings from *Case 1*. First tracing, before; second, 1 minute after; third, 6 minutes after; fourth, 66 minutes after; and fifth, 82 minutes after administration of epinephrin. Blood pressures, vascular sounds, and form and size of pulse waves, corresponding to these tracings, are shown in Table I. It will be noted that the increase in form and size of pulse wave shown in the second tracing, was not accompanied by an increase in vascular sounds or pulse pressure.

Fig. 2. Pulse tracings from *Case 9*. First tracing, before; second, 30 minutes after epinephrin. Last tracing, 9 minutes after nitroglycerine and 41 minutes after epinephrin.

A CASE SHOWING RAPID VENTRICULAR RHYTHM WITH PERIODS OF AURICULOVENTRICULAR DISSOCIATION.

By A. W. HEWLETT.

(*From the Department of Medicine, Stanford Medical School.*)

IN auriculoventricular dissociation, the auricles and ventricles beat independently, each with its own rhythm. Most cases of dissociation are due to complete heart block. The conduction of impulses from auricles to ventricles is interrupted, or, at any rate, very markedly delayed. The amount of delay necessary to produce dissociation depends in part upon the automatic ventricular rate. When this rate is rapid, an independent ventricular rhythm is more readily established as a result of delayed conduction. If the ventricular rate exceeds the sinus rate and conduction in the reverse direction is good, the rhythm of the entire heart is governed from the lower centre. Rhythms of this type, arising from the lower portion of the A-V node, have been described repeatedly. If, on the other hand, reverse conduction is poor, dissociation may result even when forward conduction from auricles to ventricles is relatively good.¹¹ A rapid ventricular rhythm may therefore favour the development of dissociation (*a*) in partial A-V block, and (*b*) where response of the whole heart would require V-A conduction.

In the following case the ventricular rate frequently exceeded the auricular rate. When this occurred the auricles usually responded to their own pacemaker, complete dissociation being the result. Conduction between auricles and ventricles was impaired: but evidence will be submitted for the belief that it was not abolished. The periods of dissociation were occasioned on the one hand by a rapid ventricular rate and on the other by impaired conduction.

Case history. Mr. E. R. S., 75 years old, entered the clinic at Lane Hospital on May the 3rd, 1922, complaining of shortness of breath. The patient stated that he had suffered from inflammatory rheumatism in 1872, and sciatica off and on for 30 years. He had had frequent sore throats during the winters, particularly during the past few years. In 1917, and again in 1919, he had been treated in the hospital for iritis.

The patient had noticed some shortness of breath for about six years. This had become more marked during the preceding six months, and had been particularly troublesome for a few weeks. During these weeks he had coughed up considerable sputum, had developed slight swelling of the feet and had suffered precordial pain on exertion.

Physical examination showed enlargement of the heart with a regular rhythm of 75 per minute. At times the heart sounds were clear, at other times an inconstant blowing diastolic murmur was heard at the apex. This was probably caused by auricular systole. The blood pressure was 175-110.

Dissociation with rapid ventricular rate. Many electrocardiograms were taken on various occasions. The ventricular complex always showed a widened *Q.R.S.* (0.12 second) and in general it suggested a lesion involving the left branch of the His bundle. *P* was always upright in lead *I*, and with one exception it was always upright or diphasic in leads *II* and *III*. Many of the tracings showed auriculoventricular dissociation, auricle and ventricle beating regularly and at different rates. In nearly all of these the ventricular rate was more rapid than the auricular rate (Fig. 3); though on one occasion the reverse was true (Fig. 4). Reference to Table I shows that the ventricular rate varied from 66 to 96, except when it was accelerated by atropin.

It is well known that in complete dissociation the ventricles usually beat regularly at a rate of 30 to 35 per minute. Rates above 60 per minute are very uncommon. A number of reported clinical examples of complete dissociation with ventricular rates in excess of 60 have been collected, and are given in Table II. It is noteworthy (1) that in most instances dissociation with a rapid ventricular rate was a transient and not a permanent condition, and (2) that in many instances drugs, and particularly those of the digitalis series, appeared to play a part in its production.

In the present case the dissociation recurred over a long period of time; it was not dependent upon the administration of drugs, and the constant deviation in the form of the ventricular complex seemed to indicate a structural lesion in the ventricles. Presumably a structural lesion was also present in the main stem (*A-V* node) of the conducting system.

A-V conduction. In Table I it will be noted that at times the auricles and ventricles beat at the same rate. At such times the ventricular contractions always occurred shortly before the auricular contractions. This regular succession of ventricular and auricular contractions suggested an excitation of the auricles from a rhythmic centre lying on the ventricular side of the *A-V* node, a suggestion supported in only one set of tracings by inversion of *P* in lead *III* (Fig. 5). In all other records (Fig. 6), *P* did not differ in form from that present when dissociation was clearly present, several transitions being recorded from dissociation to the rhythm under discussion. For this reason we conclude that in most instances the auricular contractions which regularly followed the ventricular contractions originated

TABLE I.

Rates of auricles and ventricles.

Date, 1922.	Ventricular rate.	Auricular rate.	Remarks.
May 4th	79	79	<i>P-R</i> = 0.48-0.52 of a second.
May 5th	66 78	75 78	Dissociation. Ventricles irregular.
May 6th	74	74	<i>P-R</i> = 0.48-0.60 of a second.
May 8th	84 88	73 71	Dissociation. Dissociation.
May 9th	76	76	<i>P-R</i> = 0.60 of a second.
May 11th	96 111	73 97	Before atropin. After atropin.
May 13th	88 107	70 78	Before atropin. After atropin.
Sept. 1st	83	83	Reversed rhythm. <i>R-P</i> = 0.28 of a second.
Sept. 8th	84	71	Dissociation.
Sept. 15th	75	72	Dissociation.
Sept. 22nd	77	64	After digitalis.
Sept. 27th	75	75	Digitalis continued. <i>P-R</i> = 0.60 of a second.
Oct. 2nd	71	53	Digitalis continued.
Oct. 6th	75	58	Digitalis continued.
Oct. 18th	88	62	Digitalis discontinued.
Oct. 23rd	91	61	

in the centre which governed auricular activity during the periods of dissociation. This regular succession of ventricular and auricular systoles was too enduring and too frequently repeated to be attributed to coincidence.

Two explanations might be offered for the observation that in this patient many periods occurred when the auricles and ventricles beat at the same rate and in definite sequence. According to one, the ventricular contractions, through mechanical or nervous influences, may have so accelerated a lagging auricular rate as to cause the auricular contractions to fall at a regular interval behind the ventricular contractions. That such acceleration is possible has been shown by Wilson and Robinson¹¹ and by others, who observed that in complete heart block the auricular contraction that follows a ventricular systole may be a little premature. According to the

TABLE II.

Cases of dissociation with ventricular rates in excess of 60 per minute.

Author.	Ventricular rate.	Auricular rate.	Duration.	Remarks.
Christian	64	100	Transient	Digitalis.
Christian	70	99	Transient	Digitalis.
Cortor	72	Congenital.
de Haas	78	108	Transient	Atropin effect.
Heard and Colwell ..	67-103	79-107	Intermittent	Partly but not entirely due to digitalis.
Hewlett and Barringer ..	108	101	Terminal	Digitalis.
Hunt	64	120
Lea	75	Fibrillating	..	Digitalis.
Lewis	80-90	Fibrillating	..	Digitalis.
Mackenzie	70	Fibrillating	..	Digitalis.
Routier	63-93	100-108	Transient	Rheumatic fever.
White	96	67-85	Transient	Peritonsillar abscess.
White	Over 65	43	..	Digitalis.
Windle	50-63	88	Persistent	No digitalis. Amyl nitrite did not accelerate ventricles.

other explanation, the ventricles were responding to stimuli received from the auricles. This explanation requires the assumption of a slow conduction time ($P-R = 0.48-0.60$ of a second). The latter explanation is confirmed by the premature ventricular beats which in some records occurred rather frequently during the periods of complete dissociation. In every instance these premature ventricular beats were preceded at an interval of about 0.60 of a second by a P wave (Fig. 7). At times, then, during the periods of dissociation, the ventricles responded to stimuli coming from the auricles. That they did not continue to respond was due, not to the high degree of $A-F$ block, but to the fact that the ventricular rate was more rapid than the auricular rate. Before the next auricular stimulus reached the ventricles they had responded to their own pace-maker. This they continued to do until another auricular stimulus reached them at a time when they were able to respond. White¹¹ has reported two similar observations, in which, during dissociation with the ventricular rate exceeding the auricular rate, occasional premature ventricular beats arose from impulses coming from the

auricles. In one of these cases the conduction from auricles to ventricles was good, in the other somewhat delayed.

When in our patient the automatic ventricular rhythm was slower than the auricular rhythm, a regular sequence of auricular and ventricular beats usually occurred, but, owing to delayed conduction, *P* of one heart cycle fell on or near *T* of the preceding cycle. Only on one occasion was a complete dissociation recorded in which the auricular was more rapid than the ventricular rate (Fig. 2).

Reverse conduction from ventricles to auricles was, as a rule, so depressed that the auricles failed to respond to the ventricular pacemaker

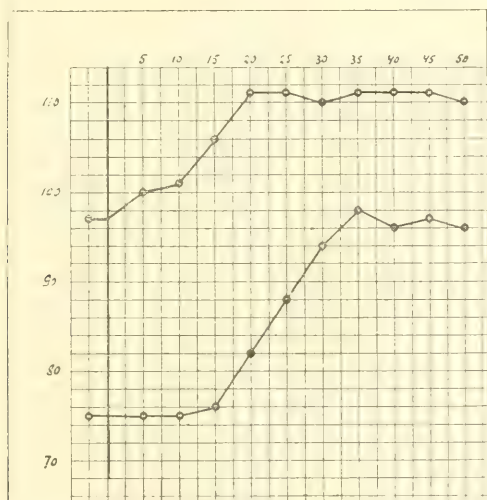


Fig. 1. Effect of injecting 1.50 grain atropin sulphate, May 11th, 1922. Abscissa indicate minutes; ordinates the rates of auricles (below) and ventricles (above).

when the latter was the more rapid. Under these circumstances, complete dissociation was the rule. A single exception to this rule was observed. On this occasion the inverted *P* suggested a control of the entire heart by the ventricular centre (Fig. 5).

Vagus effects. The ventricular rhythm in this patient was very susceptible to vagus influences. Pressure on either vagus in the neck caused a definite slowing of the ventricular rate, while the injection of atropin caused its marked acceleration. After each of two injections, the ventricular

rate increased sooner than the auricular, reaching its maximum at a time when the auricular rate had only begun to rise (Figs. 1 and 2). Evidently, in this patient, atropin released the centre governing the ventricular rate before it released the centre governing the auricular rate. This recalls the observation of Wilson,¹³ who found that, between ten and twenty minutes after the injection of atropin in normal young men, there was a tendency for an A-V rhythm to appear, and that this tendency disappeared when the full atropin effect had become manifest. Wilson's suggestion that atropin released the A-V node before it released the sinus node is supported by the present observation.

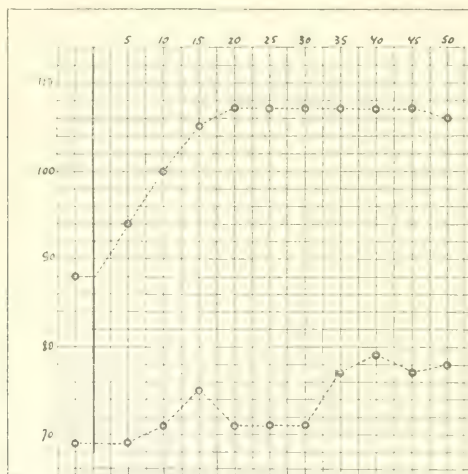


Fig. 2. Effect of injecting 1/50 gr. atropin, May 13th, 1922.

The effect of digitalis. Digitalis was given to this patient on two occasions. On May the 4th and 5th, four drachms of the tincture were given within thirty-six hours. No definite effect on the cardiac rhythm was observed. The drug was again given from September the 15th to September the 27th, at the rate of 60 minims daily. After this, 40 minims were given daily until October the 18th. As may be seen in Table I, the ventricular rate was not markedly influenced. The auricular rate, on the other hand, was definitely depressed: a minimum of 52 being recorded on October the 2nd. Evidently digitalis depressed the auricular rate more than it depressed the ventricular rate. This differential action of digitalis upon the

auricular and ventricular rate clearly favours the development of dissociation, when conduction is impaired either by digitalis or some other cause.

Dropped ventricular beats. On May the 13th, before and during the atropin effect, occasional pauses in the ventricular rhythm occurred (Fig. 8). Comparison of these pauses in several tracings showed that they bore no constant relation to the auricular rhythm, complete dissociation being present. During these pauses, the interval between ventricular beats was always somewhat less than twice the normal interval between beats. Presumably each pause was due to the dropping of a ventricular beat, owing to a block of the impulse coming from the centre which governed the ventricular rhythm. A similar observation has been recorded by White.¹²

Discussion. In the case here reported the automatic ventricular rate was unusually rapid. This was apparent in all tracings that showed dissociation between the two portions of the heart. Such a rapid ventricular rhythm suggests that the pacemaker for the ventricles was located in the *A-V* node rather than lower down in the stem of the His bundle. This suggestion is supported by the conspicuous effect of the vagus upon the ventricular rate; for it is known that rhythms arising in the *A-V* node are very susceptible to vagus influences, whereas the slow ventricular rhythm of a complete heart block is frequently uninfluenced by the vagus. The early release of the ventricular rate by atropin also corresponds with the observation by Wilson, that the *A-V* rhythm is released before the sinus rhythm. For these reasons we believe that in this patient the automatic ventricular rhythm was probably governed by the lower portion of the *A-V* node.

In the presence of such a rapid ventricular rate it is difficult to estimate the degree of conduction disturbance between the auricles and ventricles. When the ventricular pacemaker possesses a high automatic rate and is ready at any moment to assume control, ventricular beats do not drop out, and, with complete dissociation, the rapid ventricular rate makes the interpretation of all records difficult. Under these circumstances it is necessary to rely upon the *A-V* interval in estimating the conduction disturbance between auricles and ventricles. We have presented evidence which indicates that in this patient the *P-R* interval was 0.48-0.68 of a second in duration at such times as impulses crossed from auricles to ventricles. Except on one occasion, reversal in the mechanism was not observed.

The rapid ventricular rate, together with the disturbance of reversed conduction, readily explains the auriculoventricular dissociation seen in this patient. Had conduction been good, the cardiac rhythm would have been controlled either from the auricles or from the ventricles (*A-V* node), and only in the periods of transition from one to the other rhythm would there have been transient periods of dissociation. But the hindrance to reversed

conduction made dissociation possible whenever the ventricular rate exceeded the auricular. Under these circumstances the ventricular rhythm remained independent of the auricular for considerable periods: though at times it was interrupted by premature ventricular beats excited by impulses from the auricles.

CONCLUSIONS.

1. A case is reported in which a high automatic ventricular rate was associated with impaired conduction between auricles and ventricles.
2. The ventricular rate was very susceptible to vagus influences.
3. Atropin increased the ventricular rate before it increased the auricular rate.
4. Large doses of digitalis depressed the auricular rate but had no depressing effect on the ventricular rate.
5. Conduction from auricles to ventricles was not interrupted. When impulses passed, the *P-R* time was markedly prolonged.
6. Conduction from ventricles to auricles was so poor that when the ventricular rate exceeded the auricular rate, dissociation was the rule.
7. This dissociation was interrupted on various occasions by single ventricular beats, which were excited by impulses coming from the auricles.

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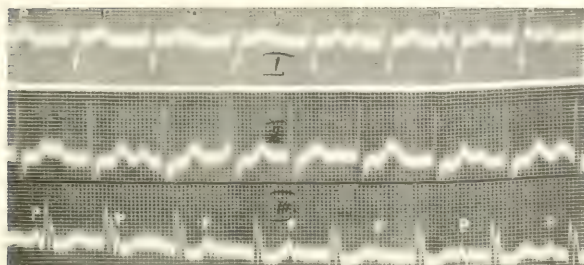


Fig. 3. Taken May 8th, 1922. Dissociation. The ventricular rate (88 per minute) exceeded the auricular rate (71 per minute). In all figures, abscissa = 0.04 of a second, ordinate = 10^{-4} volts.



Fig. 4. Taken May 5th, 1922. Lead I. Dissociation. The auricular rate (70 per minute) exceeded the ventricular rate (66 per minute).

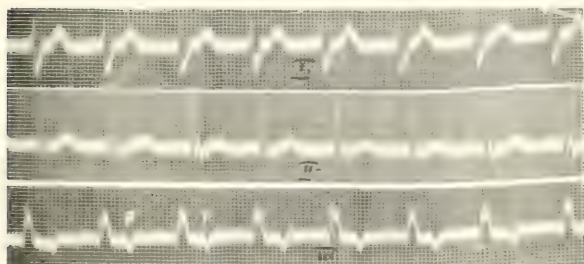


Fig. 5. Taken Sept. 1st, 1922. *P* falls regularly on *T*. *P* is inverted on *III* and positively deflected in *II* (compare with Fig. 4).

OBSERVATIONS RELATING TO SUBACUTE INFECTIVE ENDOCARDITIS.

Part 1. NOTES ON THE NORMAL STRUCTURE OF THE AORTIC VALVE.

Part 2. BICUSPID AORTIC VALVES OF CONGENITAL ORIGIN.

Part 3. BICUSPID AORTIC VALVES IN SUBACUTE INFECTIVE ENDOCARDITIS.

By THOMAS LEWIS and RONALD T. GRANT.*

(*University College Hospital Medical School.*)

Part 1.

NOTES ON THE NORMAL STRUCTURE OF THE AORTIC VALVE.

THE intimate structure of the aortic valve has been examined and described in detail on a number of previous occasions. The most accurate descriptions are to be found in the papers of Mönekeberg⁷⁵ and Dewitzky⁷¹, both of whom worked subsequent to the introduction of stains specially displaying elastic tissue. The layers of the aortic cusp belong to three categories.

The foundation of the valve, its skeleton, is a thick layer of dense connective tissue, thrown out as a continuation from the annulus fibrosus† which surrounds the aortic orifice (see Figs. 1 and 6). This fibrous layer (Fig. 6, *F. L.*) runs the length of the cusp almost to its free margin, and is the thickest of any of the layers of the valve.‡ It is clothed on its sinus side by a prolongation of the intimal layers of the aorta, and on its ventricular side by a

* Working on behalf of the Medical Research Council.

† So Dewitzky describes its connections, and with this we agree so far as the greater part of the circumference of the orifice is concerned. Mönekeberg describes it as continuous with the aortic media. The difference is largely descriptive. Not infrequently, the connective tissue of both media and adventitia are prolonged downwards and acquire an increased density. At a lower level this dense connective tissue at times shows a line of separation, which may be interpreted as representing a cleavage between that portion of it which unites with the media and that uniting with the adventitia. The former passes into the fibrous layer of the valve, the latter constitutes the chief part of the annulus. Usually, however, a line of cleavage is not seen, a single mass of dense connective tissue occupying the angle of the cusp's attachment being continuous above with the connective tissue of the media only, and sending the fibrous layer as a prolongation into the cusp.

‡ The thickest except at the valve's attachment.

prolongation of the layers of the ventricular endocardium. On the sinus side the covering is thin, so that the fibrous layer lies nearer to the sinus of Valsalva than to the ventricular cavity; the covering layers are endothelium, a very thin subendothelial layer of connective tissue, a fine sheet of elastic laminae (*s.e.*) and a thin layer of connective tissue constituting a subelastic layer. The layer which is to be emphasised for our purposes is the elastic sheet (sinus elastic layer), for it is rendered conspicuous by special elastic stains, and is traced without difficulty and without break from the aorta to the margin of the cusp. On the ventricular side the layers are a good deal thicker; they are endothelium, an easily distinguished subendothelial layer of connective tissue (*V.Sc.*), a layer of several strong elastic laminae (*V.e.*) and a subelastic layer of connective tissue (*S.*). Each of these layers is a direct continuation of the corresponding layer clothing the ventricular wall, and is prolonged onwards towards the cusp margin without break. The elastic layer (ventricular elastic layer) is again to be emphasised, because of the ease with which it is displayed by special stains and its distinctness throughout its course. The subelastic layer of ventricular connective tissue, often described in two parts, presents a notable expansion at the angle of the cusp's attachment, becoming at this point triangular in cross section and containing small blood vessels. This triangular expansion at the base of the cusp is spoken of as the intermediate layer (*I.*), or "Zwischenschicht"; its prolongation into the valve is termed the central layer of the valve (*C.L.*).

This brief summary of the valve layers suffices to bring out the salient and relevant points. More remains to be said, however, of the annulus fibrosus and of its relation to the aortic media. We have been unable to find a description of the annulus and of its limits, sufficient for our purposes. It is well known that it extends around the whole of the aortic orifice, that it sends a fibrous extension into each aortic cusp, and a similar extension into the aortic flap of the mitral valve. It is not a simple ring, for, as it passes around the aortic orifice, its level alters, following in general the lines of attachment of the cusps. This change in the level of its borders is displayed by Fig. 1. This figure is a reconstruction. A normal aorta was opened out, fixed in this position, and embedded in paraffin. Serial vertical sections (15 micron) were cut through the whole of the specimen, each tenth section being stained for elastic tissue by Weigert's method, and counter stained with van Gieson's stain. The sections were projected and separately drawn, and the diagram of Fig. 1 has been reconstructed from these drawings. The essential points in the outline of the annulus here shown have been confirmed by single sections taken through a number of normal cusps at suitable points.

Names of the cusps. The three cusps of the aorta are differently named by different writers, according to the view taken of their precise anatomical positions. The cusp from which the left coronary vessel usually arises lies most anteriorly in the body, that from which the right coronary normally

springs, lies to the right and a little behind it, and almost on the same level as the cusp which is usually without an artery. For this reason the respective cusps are often named the anterior cusp, and the right and left posterior cusps. This terminology is, to us, confusing, especially since it has not been adopted universally. Though, from a strict anatomical standpoint, it may be less sound, we prefer, for several reasons, to term the cusps, left anterior, right anterior, and posterior; the left and right valves being named to correspond with the coronary vessels which usually arise from them, and this terminology we shall retain throughout the present article.

The three commissures we name *A*, *B* and *C*, respectively: commissure *A* lying between the left and right anterior cusps: *B*, between right anterior and posterior, and *C* between posterior and left anterior cusps (see Fig. 1).

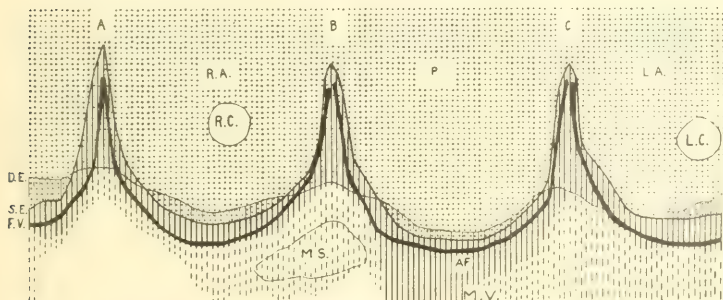


Fig. 1. A diagram of the structures supporting the normal aortic valve (2.3 times natural size). The stippling corresponds to the aortic media; where the stippling is heavy the media is superficial, where the stippling is light the media is overlapped superficially by annulus fibrosus. The unbroken vertical lines map out the annulus; where these lines are drawn thinly, the annulus is overlapped superficially by the aortic media; the broken vertical lines represent extensions of the annulus. A portion of the line *D.E.* to the right of the diagram has been lost in reproduction.

A.F. = annulus fibrosus. *F.V.* = fibrous layer of valve at its base. *L.C.* and *R.C.* = left and right coronary openings. *D.E.* and *S.E.* = deep and superficial ending of the aortic media. *M.S.* = membranous septum. *M.V.* = mitral valve. Drawn by reconstruction from serial sections.

The relation of the annulus fibrosus to these cusps and commissures is indicated in Fig. 1 by the area shaded by vertical lines: the media of the aorta is the stippled area. The black band (*F.V.*) represents the base of the fibrous layer of the valve. The upper border of the annulus and the lower border of the aortic media, end in the same lines (*D.E.* and *S.E.*). Superficially, the line (*S.E.*) along which media and annulus fibrosus meet, runs a little above the line of attachment of the cusps around the whole aorta.

Actually, the distance between the line of meeting and the attachment of the cusp varies a good deal in different hearts, and especially is this the case in the centre of the cusp. In the present instance, the distance is approximately a millimetre in the centres of the cusps: it may be and often is more, or it may be a little less. At the sides of the commissures there is usually a small but appreciable interval, though the elastic layer may (as in the case of commissures *B* and *C* here displayed, almost reach the cusp insertion. The deep junction of media and annulus follows a different line (*D.E.*). In the middle of the cusps the junction lies about $\frac{1}{2}$ to 1 mm. above the superficial junction. The junction is a bevelled one, the elastic layer being prolonged down superficially to cover the annulus for this distance (Fig. 6, *A.m.*). At the commissures this arrangement is reversed, the fibrous annulus projects upwards to form an extensive triangle, lying superficial to the aortic media. Seen in section, the junction is again a bevelled one, but the end of the media, as it thins, now lies deep. Thus, the attachment of the cusps lies throughout on the fibrous tissue of the annulus. In the centres of the cusps the whole bed is fibrous, but at the commissures it is fibrous with an underlying layer of thinning elastic media.

The lower margin of the annulus is less defined and more variable. In general it runs parallel to the valve's attachment, coming nearer to this attachment in the middles of the cusps and receding from it at the commissures. Opposite the posterior cusp it is continued downwards to form the fibrous layer of the mitral curtain. It is into the lower margin of the annulus that the muscles of the ventricle are inserted and the main annulus (unbroken lines in the figure) often sends downward processes between the masses of muscle, thereby increasing the surface of insertion (see Fig. 6). One of these processes may pass for a little distance subendocardially, and is represented in Fig. 1, under commissure *A*, by the broken extensions of the vertical lines. A similar extension, though free from muscle insertion, helps to form the membranaceous septum, which lies immediately below commissure *B*. In connection with this septum, it is to be noted that it lies wholly below the attachment of the aortic valve, and well below the lowest penetration of the elastic media.

Part II.

BICUSPID AORTIC VALVES OF CONGENITAL ORIGIN.

A condition in which the normal three cusps of the aortic valves are replaced by two, or in which two of the three cusps are separated by a low ridge or simple frænum, has long been known to occur as a congenital condition, and is commonly regarded as a rare malformation. Babes¹ states that he found it but 7 times in 10,000 autopsies. This figure probably represents the defect as rarer than it actually is; thus, de Vries⁶⁷ found 12 instances in 3,600 autopsies; we have found it three times in 215 consecutive postmortems* in which we have specially sought for it. Lesions of the kind described are to be found in considerable numbers in past reports: we have been able to collect 116 such cases^{1 to 69}; of these, 63 were males, 20 females, and in 23 the sex is not stated. But in making this collection, difficulties are soon encountered. The chief difficulty is to appreciate the reasons why individual specimens are placed in the congenital category. Generally speaking, the lesion is perfunctorily described, and in most instances a congenital origin is assumed without apparent hesitation; not very infrequently it seems clear to us that a congenital origin has been assumed when the evidence, as it is presented, is wholly insufficient; such cases have been excluded from our lists. In a number of cases the evidence appears to be quite definite; yet it is but few of the writers who, in their published accounts, mention that cusps may be fused together consequent on later but healed inflammatory disease, or by an invasion of a commissure by products of degeneration, such as calcareous deposits. This feature of the records is notable in the case of Peacock^{42 to 48}, who wrote extensively on deformities of the aortic valves, and, so we think, included, amongst a group unquestionably containing true examples of congenital malformation, numerous instances in which fusion in postnatal life would seem to be an explanation equally or more satisfactory. Now our purpose in examining this question of congenitally bicuspid aortic valves, has been to attempt to define those criteria by means of which a valve congenitally malformed may be recognised as such with certainty in adult life. We had hoped to find these criteria in past writings, but, after thoroughly examining them, came to the opinion that the story had not by any means been completed. While there is no difficulty in obtaining from past writings records of a number of unquestionable congenital cases, fully satisfactory criteria, whereby a malformed valve may be identified in adult life, and especially where such a valve has subsequently become the seat of disease, have not been found. The paucity of reliable signs is in large part due to the complete neglect of histological evidence. At a later stage such criteria as have been used, and such as we propose to add, will be discussed briefly.

* From which series all cases of subacute infective endocarditis, a disease of which we see an unusual number of instances, have been excluded.

TABLE I.

Cases of bicuspid aortic valve, congenital in origin.

Author.	Evidence of congenital malformation.	Description.
1. Rauchfuss ⁵²	Stenosis of aortic isthmus; defective V. septum, etc.	2 aortic cusps.
2. Liouville ³¹	Age 44; obliteration of aorta at isthmus.	2 aortic cusps.
3. Penock ⁴⁶ (Case 18)	Age 10 weeks. Aortic isthmus constricted. Persistent ductus Botalli.	R. A. and P. cusps, and also R. A. and L. A. cusps united by fleshy folds. Now redescribed in detail (page 30).
4. Legg ⁵³	Age 20. Obliteration of aorta at isthmus; vessels arising somewhat abnormally.	2 aortic cusps.
5. Goodhart ¹⁸	Age 27. Coarctation of aorta. (Also mitral stenosis and endocarditis.)	R. A. and L. A. adherent; tough fibrinous mass at junction.
6. Hornung ⁵²	Age 27. Obliteration of aortic isthmus. Aorta dilated and ruptured.	R. A. and L. A. fused, common commissure imperfect. Post. cusp the largest.
7. Dickinson and Fenton ¹⁵	Age 29. Coarctation of aorta.	2 cusps; ant. and post.; coronaries both arise from posterior.
8. Kriegel ²⁶	Age 11. Coarctation of aorta.	2 well formed aortic cusps.
9. Sommerbrodt ⁵	Age 40. Coarctation of aorta.	2 aortic cusps. The one (L. A.) dilated; the other formed by union of R. A. and P. cusps. Much diseased.
10. De Vries ⁵	Age 3. Stenosis of aortic isthmus; persistent ductus Botalli.	Probable union of R. A. and L. A.; a low ridge separates them. Fresh endocarditis present.
11. Brettel ⁹ (Case 1)	Age 17. Stenosis of aortic isthmus, etc. Aortic aneurisms and rupture.	R. A. and L. A. fused, a low ridge separating them. Combined cusp the larger.
12. Rokitsky ⁵⁵ (S. 14, Case 11)	Newborn. 2 pulmonary cusps; V. septum defective. Anomalies of vessels.	2 aortic cusps placed ant. and post., from each of which a coronary artery springs.
13. Rauchfuss ⁵	Age 3. Defective commissure between 2 pulmonary cusps.	2 aortic cusps, one to right and one to left.
14. Osler ⁴⁰ (Case 7)	8 months' foetus. 2 pulmonary cusps and 1 rudimentary. Defective V. septum, and abnormal origin of vessels.	2 aortic cusps, one placed to the right and a little the larger, divided by a raphe; the other to the left. Rt. coronary springs from right cusp.
15. v. Arn ³ (Case 4)	Age 50. 2 pulmonary cusps, defective V. septum.	2 aortic cusps. Calcified vegetations, perforation, etc.
16. Thérémim ⁴³ (Page 159)	2 pulmonary cusps. Persistent ductus Botalli.	2 aortic cusps of equal size, one in front and to the right, the other behind and to the left. A coronary springs from the middle of each.
17. Tirard ⁶³	Age 5 months. Four pulmonary cusps. V. septum patent.	2 aortic cusps the ant. of which gives off both coronaries.
18. Lochter ⁵⁸	Foetus, Cor. biloculare. 2 pulmonary cusps, etc.	2 aortic valves, irregularly formed.
19. Sibbald ⁵⁶	Age 10 months. Pulmonary stenosis. Defective V. septum, etc.	2 aortic cusps. Placed to right and left.

SUBACUTE INFECTIVE ENDOCARDITIS. 27

TABLE I.—*Continued.*

Author.	Evidence of congenital malformation.	Description.
20. Bouillaud ⁸	Age 39. Pulmonary stenosis. Absent <i>V. septum</i> , etc.	2 aortic cusps, one divided by a "flet." Placed ant. and post. Cusps much thickened.
21. Mönckeberg ¹⁷	Age 3 days. Abnormal basal vessels; left ventricle diminutive.	Fusion of <i>R. A.</i> and <i>L. A.</i> , and of <i>R. A.</i> and <i>P.</i> cusps to form a diaphragm. The lines of union marked by ridges.
22. Smith ¹⁸	Age 5 hours. Rudimentary left ventricle; pulmonary artery passes into descending aorta.	2 aortic cusps.
23. Dilg ¹⁶	Age 2. Subaortic stenosis and persistent left sup. cava.	2 aortic cusps, one, a little the larger, divided by a raphé and giving origin to both coronary arteries.
24. Brettel ¹⁹ (Case 8)	Age 4. Persistent superior cava.	2 equal cusps, no subdivision; each gives off a coronary artery. Cusps to right and left.
25. Preisz ²⁰	Stillborn; cyclops; ductus arteriosus of unusual size. <i>V. septum</i> defective.	2 cusps, the larger in front and to right, the other behind and to left. A coronary arising from each. Almost certainly union of <i>R. A.</i> and <i>P.</i>
26. Preisz ²⁰	Age 4 days. <i>V. septum</i> defective, etc..	2 cusps, the larger behind and to left is divided by a small aortic ridge, the other in front and to right. A coronary arising from each. Union of <i>L. A.</i> & <i>P.</i>
27. Hare ²⁰	Age 14 months. <i>V. septum</i> defective.	3 cusps of almost equal size, fusion of a pair, and partial fusion of another pair.
28. Obre ²⁰	Age 6 weeks.	2 aortic cusps equal in size, no sign of subdivision. A coronary springs from each.
29. Quain ²¹	Age 6 months.	2 aortic cusps, one 1·6 times the size of the other shows evidence of subdivision and gives off both coronary arteries.
30. Lloyd ²²	Age 13 months.	2 aortic cusps. One, divided by an indistinct ridge, is double the size of other. Cusps red, rough and hard and puckered.
31. Great Ormond St. Museum (Case 209)	Age 4 10/12.	2 aortic cusps* undivided. Almost equal in size. A coronary artery arising from each.
32. Ditto (Case 211)	Age 3.	Fusion of <i>R. A.</i> and <i>P.</i> cusps, low frenum separating them. Divided cusp somewhat the larger.
33. Ditto (Case 220)	Age 3 1/3.	Fusion of <i>R. A.</i> and <i>P.</i> Probably undivided. The combined cusp somewhat the larger.

* In none of these three last cases was there more than a little thickening of the malformed cusps.

One method of approach, not yet adopted, is to sort out from the group those cases which are not in doubt, namely, instances in which the aortic defect is associated with other congenital malformations of the heart, and instances occurring in very young children. If, for the last purpose, the age limit of five years is taken, and valves diseased or extensively thickened, are excluded, 30 cases are on record*, and to these, through the kindness of Dr. Wilfred Pearson, we are able to add three instances, specimens now in the museum of the Great Ormond Street Hospital. The relevant information in respect of these 33 cases is summed up in the previous table (Table I). In 27 of the 33 cases other congenital anomalies are described. The commonest associated malformation is constriction or coarctation of the aorta, occurring in no less than 11 or 33 per cent. of the cases (*Cases* 1-11). In 7 cases the pulmonary valve presented a simultaneous anomaly in the division of its cusps, with or without other congenital defects. In 2 cases, a pulmonary stenosis was found (*Cases* 19-20). In 4 cases the basal vessels showed an anomaly of development (*Cases* 21-24): in 3 cases the ventricular septum was defective (*Cases* 25-27). In the last 6 cases tabulated (*Cases* 28-33), no other congenital defect is noted, but the age was under 5 years.

If we are rigid and confine ourselves to this material, almost the sole information, at present available respecting the characters of congenital bicuspid valves, is contained in the last column of the table. It may be summed up as follows:—

Cusps affected. The left and right anterior cusps were united in 3, and probably, in 6 cases, the right anterior and posterior in 4 cases, and the posterior and left anterior in 1 case. In 2 additional cases, both the left and right anterior, and the right anterior and posterior cusps were united. In 20 cases it is impossible to state which cusps were affected; in most of the last instances the valve is described as consisting of 2 cusps, and the note may be added that they were placed to right and left, or anteriorly and posteriorly. It would appear from these figures that fusion is most frequent between the right anterior and left anterior cusps, a conclusion borne out by further observations; but it is by no means confined to these two, fusion between the right anterior and posterior cusps being almost as frequent.

Subdivision. Of the 33 malformed valves, in 13 instances a ridge, frænum or raphe is described as subdividing one of the two cusps. In 3 instances it is stated that there was no subdivision of either cusp, in one instance it is stated that there was probably no such subdivision; in 16 cases no statement is made, though we may infer that in many of these instances there was no subdivision. Thus, in about half the cases, possibly more than half the cases, the line of fusion of two cusps was distinct; in the remainder there was no subdivision.

* Patency of the foramen ovale, if accepted as evidence, would add one or two to this number.

Size of cusps. Lastly, it is clear, from the notes, that there may be inequality in the sizes of the malformed cusps. The rule appears to be that a partially subdivided cusp is the larger of the two; but it is also to be gathered that it is not twice the size of the undivided cusp.

If to these 33 undoubted congenital cases, we add the remaining 83 described as congenital, and almost certainly mainly congenital, we obtain the following statistical statements.

TABLE II.
Frequency of cusps affected.

	Fusion of				Unknown.
	L. A. and R. A.	R. A. and P.	P. and L. A.	L. A. and R. A. R. A. & P.	
33 congenital cases	3 (3)*	4	1	2	20
83 cases (mostly congenital) ..	27 (7)	11 (4)	2 (3)	0	29
116 cases	30 (10)	15 (4)	3 (3)	2	49

Subdivision.

	One cusp subdivided.	Stated to be no division.	Subdivision not mentioned.
33 congenital cases	13	3 (1)	16
83 cases (mostly congenital) ..	54 (4)*	7	18
116 cases	67 (4)	10 (1)	34

* The figures placed in brackets are additional cases in which the evidence is not quite conclusive.

The combined figures serve to emphasise the frequency with which the right and left anterior cusps are fused. They serve also to stress the frequency with which partial subdivision of one cusp is discovered. It is to be remembered, however, that the combined figures are to be regarded broadly and with a little reserve; the 83 added cases are almost all adult cases, and in very many of these the cusps were the site of inflammatory disease, recent or old, or of gross degenerative change: nearly all were thickened. In the notes of these 83 cases, measurements of the cusps are not infrequently given, and the conclusion reached from the 33 congenital cases is confirmed from them. Déteindre¹⁴ sums up the position by stating that the subdivided cusp is larger than 1 normal cusp, but smaller than 2 normal cusps; a statement which is borne out by most of the measurements given.

We shall next describe four cases of our own in some detail.

Case 1. PEACOCK'S CASE; CONGENITAL FUSION OF *L.A.* AND *R.A.*, AND *R.A.* AND *P.* CUSPS.

This heart is from a child of 10 weeks, described by Peacock, and figured by him (Plate viii., Fig. 1.) in his "Malformations of the Heart."¹⁶ This figure is an excellent reproduction of the original drawing, which is in the possession of the City of London Hospital. The specimen is now in the museum of the Royal College of Surgeons, London. The aortic valve is described by Peacock (page 152), in the following words: "The aortic was much larger than the pulmonic orifice: and there appeared to be only two valves at its aperture. The largest of them was, however, obviously formed by the fusion together of two of the segments." His figure, which illustrates the specimen from the same angle as our photograph (Fig. 8), shows a single large and distinct cusp to the left, and two smaller cusps, fused together, but separated by a deep septum, to the right.

Through the kindness of Sir Arthur Keith, we are able to redescribe the specimen. The aorta is narrowed down from the point where the innominate artery leaves it, for a distance of 7 mm. beyond the origin of the subclavian artery, the total length of the narrowed portion being 15 mm.: the narrowing is considerable. The ductus arteriosus, which is not shown in the figure, is widely patent.

The first portion of the aorta is dilated, and the aortic valves are deformed. There are three aortic cusps, and these, from left to right in the figure, are the left anterior (*L.A.*), the right anterior (*R.A.*), and the posterior (*P.*). The coronary arteries spring in normal fashion from the first two of these cusps. The three cusps are equal in size, and not unequal as Peacock figures them. Measured along the borders of the sinuses of Valsalva, from the beginning of one commissure to the next, their breadths are 9.5, 9.0 and 8.5 mm. respectively.* The right anterior and posterior cusps are united (commissure *B*) as stated by Peacock: but the right and left anterior cusps are also united (commissure *A*). The cut which opens the aorta passes near to the union of the posterior and left anterior cusps (commissure *C*), leaving the end of the posterior cusp attached to the left edge of the opened aorta (as this is figured).

The left anterior cusp is a little thickened throughout the whole of its free margin, and the thickening extends nearly half way down to the line of the cusp's insertion. From the centre point of the cusp the free edge is more conspicuously thickened into a fleshy fold (*lf.*), which passes under a similar fleshy fold (*rf.*) coming from the right anterior cusp, and terminates in the corresponding commissure (*A*). This commissure starts as a smooth ridge, which soon divides into two rounded smooth ridges of smaller diameter, which separate as they descend and outline a small triangle whose floor is filled; it is into the under surface of this floor that the fleshy fold, marking

* Measurements subsequently stated have all been taken similarly.

the free edge of the left anterior cusp is inserted. The commissure, from the beginning of its ridge to the base of the triangle, measures 3 mm. But the two cusps are united for a further distance of 1.5 mm. by the fleshy fold from the right anterior cusp; this fold passes across the commissure, and is firmly bound to it and to the fold from the left anterior cusp, and ends by being inserted into the aortic surface of the left anterior cusp a little way past the free margin of the cusp. The right anterior cusp is much thickened along its free margin. In its centre the somewhat irregular fleshy edge has a thickness of 1.5 mm. The thickened edge is continued into the fold which crosses commissure *A*, as previously described. There are also irregular thickenings on the floor of this cusp towards commissure *B*. This commissure begins as a smooth ridge of aortic wall of about 5 mm. extent; it is continued for approximately 3 mm. further as a sharper and narrower ridge which flattens out before it reaches the edge of the valve at a rounded incisure (*i*). Where the main ridge of the commissure diminishes in breadth, just above the cusp's line of attachment, a small fold (*f*) runs off from it to be lost in the irregular thickening of the floor of the right anterior cusp. The commissure is depressed below the levels of the adjacent valve margins, so that the two cusps tend to be thrown into one, though partially subdivided by the irregular central floor.

The posterior cusp is irregularly thickened throughout. The most prominent thickening is a raised patch on the ventricular side near its centre. Its free margin is thickened and rounded throughout; its thickness is a full millimetre where it runs into commissure *B*. The remnant of this cusp attached to commissure *C* is irregularly thickened at its edge. Commissure *C* is not fused, its abnormality consisting solely in the thickening of the margins of the cusps which constitute it.

To summarise, scarcely any portion of the aortic valve is normal. There is conspicuous thickening of the valve margins throughout their extent, an irregular and fleshy thickening. Two out of the three commissures are united for a considerable distance.

The more interesting of the two commissures is, perhaps, commissure *A*, where the edges of the corresponding valves are greatly thickened into smooth intertwining folds. The appearance of the upper portion of this commissure with its two diverging ridges, suggests that these ridges may represent what would become in normal development the two valve margins; but this idea is not borne out by their relation to the actual cusp edges; for the ridges are not continued into the latter. In the absence of a microscopic examination of this region, no more can be said than that the commissure presents a gross and intricate deformity, the details of which, owing to the small size of the heart, appear to have escaped Peacock's notice. It is difficult to conceive how such a deformity could have arisen as a result of inflammatory disease; its appearance strongly suggests an error in the outgrowth or division of the original endocardial cushions.

Microscopic examination.

This specimen has an historic value, and we have not felt justified in making more than a very limited histological examination of it. Two small portions of tissue have been removed; a small square block from commissure *B* and a portion of the remnant of the posterior cusp attached to commissure *C*. *Commissure B.* The block of tissue includes the lower portion of the main ridge (*r*), and the upper portion of its continuation in the narrower ridge with the fold *f*. The incisions which removed this block of tissue penetrated to the ventricular surfaces of the cusps below, allowing the whole thickness of the cusps to be examined. The sections were cut serially through the whole block from above downwards at right angles to the main ridge, and sections were stained alternately with hæmatoxylin and eosin, and with Weigert's elastic stain. In the uppermost of these cross sections, the main ridge consists chiefly of the aortic media, most of the elastic laminae passing almost continuously across the ridge; in the centre of sections through the ridge, the horizontal arrangement of the elastic laminae is disturbed, the laminae are whorled, and many more fibres than usual are seen to be cut in cross section. This simple whorling continues in the ridge to a point nearly 5 mm. below its origin. The disturbance increases as the sections are further followed down the commissure, and the elastic elements become sparser in the next millimetre of tissue. This brings us almost to the insertion of the cusps. The aorta media becomes replaced by relatively dense, but nucleated, connective tissue which shows the same type of whorling, the deepest lying elastic laminae soon being lost altogether, though the superficial fibres are continued almost a millimetre further. This upward projection of connective tissue into the media of the aorta takes place in a fashion the reverse of normal; it is overlaid by the last of the medial elastic tissue. The connective tissue is a projection from a larger mass of similar tissue which lies at a lower level and clearly represents the young annulus fibrosus. In brief, the arrangement of the media and fibrous ring in the ridge differs in two respects from what is found in normal commissures; the pure connective tissue of the annulus terminates in the commissure at an unusually low level, and secondly, the bevelled union between the media and annulus is reversed, the superficial ending of the elastic layer coming lower down than its deep ending.

A further distinctive character begins to appear at a lower level, namely, when the main ridge of the commissure (*r*) loses its breadth, and the subsidiary fold (*f*) makes its appearance. Near this level the sections pass completely through the valve cusps, and include their ventricular surfaces, so that the separate layers of the cusps are clearly displayed.

An illustrative cross section, the position of which is displayed by the line in Fig. 8, is given in Fig. 9. A portion of the aortic media is shown to the right; it is the termination of the media, the convex edge of which projects downwards into the sinus of the right anterior cusp. The subsidiary

fold (*f* in Fig. 8) is seen directly to its left in Fig. 9 *f*; this fold, in fact, marks the lower limit of the aortic media in the sinus. It is formed of a ridge of the annulus fibrosus (*An.f.*). The point where the cusps should separate is marked by the narrowed continuation of the main ridge (*r* in Fig. 8); this ridge is seen as an undercut projection in the section (Fig. 9 *r*). This ridge lies above a central space in the figure; the latter is the normal upward projection of the ventricular cavity at the commissure. The commissural space is lined by endocardium, which is continuous around the whole space, and consists of two chief layers, a conspicuous layer of strong wavy elastic laminae (*V.e.*) and superficial to this a thickened subendothelial layer (*V.s.*). On the upper side of the space (in the figure) these two layers form the ventricular layers of the fused cusps. The chief layer of the cusps (*f.l.*), is continuous with the annulus fibrosus (*An.f.*), and corresponds to the chief or fibrous layer of the valve in normal adults. It consists of densely packed wavy fibres in which numerous round and oval nuclei are to be seen. Its histological details are very similar to those found in the corresponding layer of the cusp in the child at birth and shortly after birth*. More superficially are three remaining layers. A layer of open meshed connective tissue, containing numerous spindle-shaped nuclei, the nuclei and fibres being arranged for the most part horizontally. This layer probably represents the normal sinus subelastic layer. Next to this is a very thin layer of elastic tissue (*S.e.*) continuously traced across the whole section and to the right into the superficial elastic layer of the aorta. It corresponds to the normal sinus elastic layer. It is covered in turn by a thick cushion of open meshed connective tissue (*S.s.*), whose fibres pursue different directions and interlace; this connective tissue is richly nucleated, the nuclei being circular in cross section, large and oval in long section, and surrounded by a scanty protoplasm, which ends in processes continuing into the fibres of the matrix. This tissue corresponds in its structure very closely to foetal connective tissue, such as is correctly described in the valves of the foetus by Dewitzky⁷¹. On the ridge it corresponds to a much thickened sinus subendothelial layer: to the sides of the section it is traced as a much thinner layer which covers the sinus elastic layer.

Briefly, the distinguishable layers of the cusps occur in the following order: sinus subendothelial layer, sinus elastic layer, subelastic layer, main fibrous layer, ventricular elastic layer, ventricular subendothelial layer. These layers are the normal layers of the valve, and each of these layers is continued without break across the commissure. There is no evidence of inflammation, past or present. These observations stamp the deformity as a congenital malformation, for they clearly show that the two cusps have been laid down in one sheet without subdivision. The continuous arrangement of the layers across the commissure is in sharp contrast to what is observed in cusps which have fused as a direct consequence of an inflammatory process, as will be seen at a later stage.

* A statement based on a comparison of the tissue with those from several hearts of children of the same or similar ages.

The remnant of the posterior cusp attached to the commissure *C* was examined histologically, because it allowed us further to explore the thickenings of the valve margins in this case without unduly damaging the specimen. In the sections all the layers of the cusp are well displayed. The thin sinus elastic layer is distinct: the main fibrous layer of the valve is, perhaps, a little thicker than normal: it is constituted of tissue elements identical with those of the main fibrous layer in commissure *B*. The central layer of the cusp is well developed, as is also the ventricular elastic layer. The last is covered by a very thickened ventricular subendothelial layer, which is mainly responsible for the thickening of the cusp. Some of this thickened layer consists of rows of fibres arranged parallel to the margin of the cusp, none too compact, and having numerous spindle shaped cells carrying well-developed oval nuclei; in other places the groundwork of fibres is more meshed; this tissue being identical in appearance with that of the sinus and ventricular subendothelial layers at commissure *B* (fetal connective tissue). It is pervaded by very fine and scattered elastic fibres.

These sections, and those at commissure *B*, demonstrate that the thickening of the valve cusps is due to an excess of subendothelial tissue (in part the sinus, and in part, the ventricular layer); in nature, this thickening is distinct from what is found after inflammatory disease; the cellular elements and their arrangement are those normally found in the valves at or about the time of birth.

Case 2. CONGENITAL FUSION OF R.A. AND P. CUSPS.

For the second case to be described, we are indebted to Professor Elliott Smith. The specimen is one which has been, for many years, in the anatomical museum at University College, and no details of the patient's history or manner of death are available. The specimen was evidently taken from an adult, and probably from a middle-aged or elderly subject. A photograph of the aortic valve is shown in Fig. 14, and a cross section of the basal arteries, drawn accurately to scale, is given in Fig. 4. One cusp (*L.A.*) lies to the left and in front, and near its centre is the opening of the left coronary vessel; this cusp measures 31 mm. The other cusp (*R.A.* and *P.*) lies to the right and behind, and from its anterior portion gives origin to the right coronary vessel. It is the larger, measuring 37 mm., and shows, externally or internally, no trace of subdivision. The membranaceous septum is placed opposite the centre of this cusp, and its lateral limits* are shown in the diagram: a portion of this septum projects upwards, and appears on the sinus side of the cusp. From the anatomical relations of

* The limits of the membranaceous septum were fixed by holding the septum to the light and marking off the translucent area, in most specimens; in cases of difficulty the limits were fixed by means of serial sections.

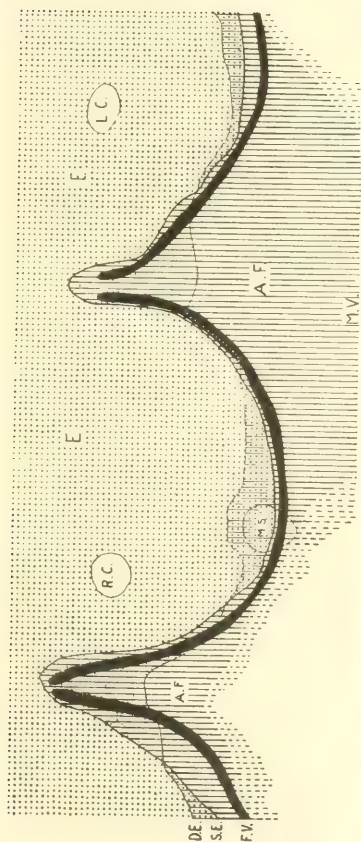


Fig. 2. (Case 2.) A diagram of the structures supporting a congenitally bicuspid aortic valve (a little less than twice natural size). Drawn by reconstruction, and lettered in the same way as Fig. 1. *E* - elastic media of aorta.

these cusps it is probable that the smaller represents the normal left anterior cusp and the larger the right anterior and posterior. The cusps are a little thicker and therefore less translucent than normal valves in all their parts; the two commissures *A* and *C* are widened by separation of the cusp attachments, and below each there are some small thickenings of the endocardium on the adjoining sides of the cusps.

The remainder of the heart, including the mitral valve, is normal, with the exception of a few small patches of atheroma in the base of the aorta.

The aortic valve was opened out and cut in serial vertical sections, each tenth section being stained in the usual fashion. The reconstructed diagram is shown in Fig. 2, which is drawn on the same plan as Fig. 1. From this diagram it is at once apparent that the two commissures are normal, architecturally. The smaller cusp, that which has been divided in opening the aorta, is built normally throughout. In the larger cusp, the superficial termination of the media follows closely the line of the cusp's attachment, sweeping smoothly from one commissure to the other, and approaching very closely to the line of attachment at all points. The line of the deep termination of the media is disturbed at its centre by the membranaceous septum, which projects above the line of the cusp's attachment. The position of the septum in respect of level, and in relation to lateral landmarks, is normal. It falls inside the cusp, because the normal commissure expected at this point is absent, and the triangle which the membrane would naturally occupy is included in the full sweep of the combined cusp's attachment.

The annulus fibrosus of the heart is throughout thicker than normal; its extent in an upward and downward direction is shown in the figure. Its upper limits are modified in the neighbourhood of the membranaceous septum to correspond with the lower limits of the aortic media. Thus, it extends higher above the line of the cusp's attachment than would be expected in a normal cusp, but otherwise it is related to the media in the same fashion as is the normal annulus; that is to say, it lies deep to the overlapping media.

In brief, commissure *B*, of this aortic valve, is wholly lacking; it is lacking because the aortic media has come to occupy in this region an unusually low position, so low that it largely covers the membranaceous septum, and because the usual upward and superficial extension of the annulus has failed.

Case 3. CONGENITAL PARTIAL FUSION OF *R.A.* AND *L.A.* CUSPS.

F. E., a man of 31 years, was admitted to hospital in July, 1922, and gave the following history:—

He served during the war and was wounded in 1916 in the leg and shoulder. He was discharged from the army in January, 1918, apparently in a healthy condition. A year before admission he was treated for tuberculous glands in the neck; for some months he had coughed and expectorated a great deal; during a few months prior to admission, hoarseness, pains in the throat and progressive weakness had been noticed. On admission, he was found to be suffering from advanced pulmonary and laryngeal tuberculosis, from which he succumbed in three weeks. The heart presented no signs of enlargement; the heart sounds were normal.

Pathological changes.

General. An emaciated body. The *lungs* are covered by recent lymph; at the apex of each lung is a tuberculous cavity, and the rest of the upper lobe on each side is involved by caseous masses and small tubercles. The lower lobes are consolidated, being closely studded with small grey tubercles. The *larynx* presents early signs of involvement. *Ileum.* There are numerous large tubercular ulcers in the small bowel. The *kidneys* contain a few small tubercles in their substance. The remaining abdominal organs are normal. The *heart* weighs 272 grammes and the pericardium is healthy. The cavities are not enlarged, neither are their walls thickened. The *pulmonary* valve is normal; the tricuspid valve shows a little irregular nodular thickening at its margin. The *aorta* is normal, with the exception of a few small patches of atheroma collected especially around the border of one sinus of Valsalva. The *mitral* valve is normal but for an area of thickening presently to be described, and but for a few small atheromatous patches in the base of its aortic flap.

The *aortic valve* (Figs. 4 and 15) is abnormal, the right (*R.A.*) and left (*L.A.*) anterior cusps being fused together, though subdivided by a low ridge (*r*, Fig. 15). The undivided cusp corresponds to the posterior cusp (*P*) of the normal valve, and measures 38 mm. This cusp is not only of unusual size, but its line of attachment, relative to the mitral valve, is increased, for commissure *C* falls, not as is usual near the centre of the mitral valve, but opposite its margin (see Fig. 15). The width of the membranaceous septum is also much increased; its relation to the cusps is shown in Fig. 4. The combined cusp, similarly measured, is of 40 mm. extent, equally sub-divided by the sinus ridge: the right and left coronary vessels arise from the two subdivisions of this cusp.

The cusps are both thickened in all parts; their margins are thickened irregularly; other irregular linear thickenings are to be observed along the lines of apposition of the cusps. Commissure *B* begins as a yellow smooth ridge, 6 mm. long, from the end of which the margins of the cusps spring. Commissure *C* is slightly adherent. Upon the posterior cusp, near its junction with the left anterior cusp, an opaque and raised area of irregular thickening involves the body of the cusp and extends well over its margin of attachment to involve the aortic cusp of the mitral (Fig. 15, *f*).

On section, the thickening of the cusp is found to lie almost exclusively superficial to the main ventricular elastic layer, and to involve therefore, chiefly, the ventricular subendothelial layer.* The thickening which extends on to the mitral valve is similarly related to the valve layers, and is due to an increase in connective tissue, this being compact and relatively sparsely nucleated, and heavily invaded by fine and coarse wavy elastic fibres throughout: the nuclei are for the most part flattened. The connective tissue forming the most superficial layers of the plaque of thickening (Fig. 15, *f*) is alone of rather younger appearance. The central layer of the cusps is well developed and somewhat more vascular than normal. No infiltration is seen in the cusps.

* An early degree of annular sclerosis, affecting the fibrous layer of the valve at its attachment is not described, as it is almost usual in a man of this age (Mönckeberg, Dewitzky).

A smooth and rounded ridge (*r*) extends from the margin of the sinus down to and well on to the combined cusp. The length of this ridge from the border of the sinus to the cusp's attachment is 14 mm., its breadth about 2.5 mm., and its height approximately 1.5 mm.. On the ventricular side the combined cusp presents a distinct triangular break in the otherwise continuous sweep of its line of attachment. A few millimetres after reaching the level of the apex of this triangular depression, the main ridge (*r*) sends off two lateral processes which proceed further into the right and left cusps (see Fig. 15). These subsidiary ridges do not proceed to the valve margin, as does the main or central ridge, but turn and run laterally in the cusps and almost parallel to the margins, ending somewhat abruptly about 3 mm. from the latter.

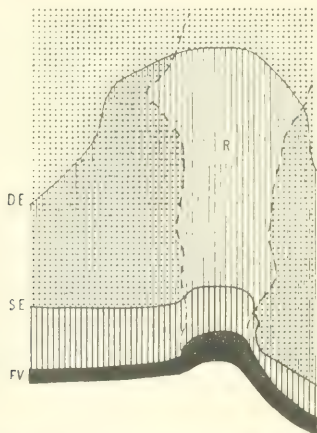


Fig. 3. (*Case 4*.) A diagram of the structure supporting a congenitally defective commissure (5 times natural size). Drawn by reconstruction and lettered as in Figs. 1 and 2.

R = main ridge representing commissure; over the area of thin vertical lines and fine stippling, the elastic elements of the media are whorled.

The ridge was excised and serial sections cut of it horizontally from top to bottom,* sections being taken at regular intervals, mounted and stained. Fig. 3 is a reconstruction of the region of the main ridge, down to the level of the cusp's line of attachment. The media extends almost as far as the cusp's attachment throughout the whole region of the ridge, its superficial termination (*S.E.*) running parallel to the line of the cusp's attachment (*F.V.*). Deep to this elastic media, the annulus fibrosus sends a broad tongue

* Owing to the manner in which the aorta was opened, the top 2 mm. of the ridge was not included in the serial sections.

shaped projection upwards, and this reaches a point 3 mm. from the beginning of the ridge. The ridge itself contains abundant elastic tissue except over a short part of its course immediately above the attachment of the cusp, but the arrangement of the elastic elements here differs from that seen at the sides of the ridge, where the sections show uninterrupted laminae. In the ridge the elastic elements are less numerous, and become less and less so as the ridge descends, and are whorled, many fibres being cut in cross section. This whorling is continued throughout the length of the ridge to the *S.E.* line below, and is seen to a lesser extent for a short distance above the deep termination of media (*D.E.*). The annulus fibrosus forms the deep layers of the ridge. Thus the meeting of media and annulus is a long bevelled joint, the superficial bevel consisting of media, while the deep bevel consists of annulus. The relation is again the reverse of that found at a normal commissure, but is the same as that found in the centre of a normal cusp: in this respect the specimen resembles commissure *B* of *Case 1*. It resembles the last in another respect, namely, in the long continuation of whorled elastic elements in the main ridge: it differs from the last in the unusual extent of the reversed overlap. The sections falling below line *S.E.* show the ridge to consist of a simple thickening of the annulus fibrosus. Beyond the level of the combined cusp's attachment the serial transverse sections show the structure of the cusp from the line of its attachment to its margin: all the chief normal layers of the cusp are intact. The central portion of such a section, falling well towards the valve's margin, and including the main ridge, is shown in Fig. 11. It displays the expansion of the fibrous layer (*f.l.*) to form the main ridge (*m.r.*): it shows this ridge to be covered by the continuous sinus elastic layer (*s.e.*) on the aortic side: and by an ill-defined central layer, a well-defined and unbroken ventricular elastic layer (*V.e.*), and a very thickened but continuous ventricular subendothelial layer (*V.Se.*) on the ventricular side.

Apart from the thickening of the last-named layer, a thickening which, judging from its high content of fine elastic fibres, and its relatively sparse and flattened nuclei, is not of recent origin, no sign which can be interpreted as recent or old inflammation* exists in any part of the sinus or cusp portions of the ridge or surrounding tissue.

The abnormal arrangement of the tissue layers in the ill-formed commissure, and the continuity of the layers throughout the combined cusp, stamps the defect as a congenital malformation: for it is clear that the tissues have been laid down in this fashion, as it was clear in the cases previously described.

* The thickening of the ventricular subendothelial layer, and the thickening marked *f* in Fig. 15, do not themselves imply inflammation. Such thickenings are usually considered to occur as secondary processes in aortic valve margins which fail closely to adjust themselves when the valve shuts; they are the rule rather than the exception in specimens such as that described.

This specimen, and the last, may be viewed together as illustrating separate stages of the same type of arrested development. In *Case 2* there has been little or no attempt towards the formation of a commissure: in the present example the development has proceeded a little way before arrest has happened.

Case 4. CONGENITAL PARTIAL FUSION OF R.A. AND P. CUSPS: ANNULAR SCLEROSIS OF THE VALVE.

W. C., a chamber-sweep, aged 68, was admitted to hospital on November the 20th, 1922, in a moribund state. He had suffered from shortness of breath and cough for eight months, having previously "been healthy," and when admitted presented signs of general venous stasis and edema, a right pleural effusion, enlargement of the heart and fibrillation of the auricles.

The aortic sounds were normal. A systolic murmur was heard at the apex. The patient died on the seventh day after admission.

Pathological changes.

General. Edema of the legs is present. The right pleura contains several pints of clear fluid. The abdominal organs are congested. *Kidneys.* One kidney is normal, the other much reduced in size. Both are finely granular on the surface.

The heart weighs 466 grammes. On the visceral pericardium of the right ventricle are many large milk spots. Both ventricles are hypertrophied and dilated, the left chamber especially. The left auricle is dilated. The *pulmonary valve* is large, the anterior cusp especially so (see Fig. 4). The attachments of the cusps show very early annular sclerosis, and the noduli are a little thickened. The *tricuspid valve* is normal but for some age thickening of its margin. The *aorta* is larger than normal and its lining presents many small atheromatous deposits, accumulated particularly along the borders of the sinuses. The coronary vessels arise normally. *The ventricular septum.* Below the aortic valves, and at a distance of 3 centimetres from them, a number of dense endocardial thickenings occur. These are circumscribed, raised, and of a cream white colour. They are extensive and involve much of the septum and of the endocardium surrounding the anterior papillary muscle. The thickening consists of dense connective tissue, pervaded by minute elastic fibres and showing no sign of active inflammation. The *mitral valve* is normal, except for the presence of a few superficial atheromatous deposits on the ventricular aspect of its aortic cusp. The endocardium of the left auricle is opaque, especially on the posterior wall of the auricle; but not very unusually so.

The *aortic cusps* are two in number (Figs. 4 and 16). One cusp, from which the left coronary vessel springs, lies in front and to the left, and represents the normal left anterior cusp: it measures 51 mm. The other lies to the right and behind, and is partly subdivided by a ridge into two compartments, from the anterior of which the right coronary springs; this subdivided cusp measures 56 mm., and represents the normal right anterior (27 mm.) and the posterior cusps (29 mm.), the base of the mitral valve being attached to the latter and to the left anterior cusp.

The subdividing ridge starts at the border of the sinus, but is only just perceptible for the first 8 mm. of its course, as a broad and smooth elevation. It then increases somewhat abruptly in prominence, and is continued as a dense cord of whitish tissue, the smooth surface of which is broken by calcareous deposits; at its origin this prominent ridge (Fig. 16*r*) is flanked by two broken chains of whitish calcareous nodules. These chains diverge a little when the cusp is reached, and are carried onwards to within about

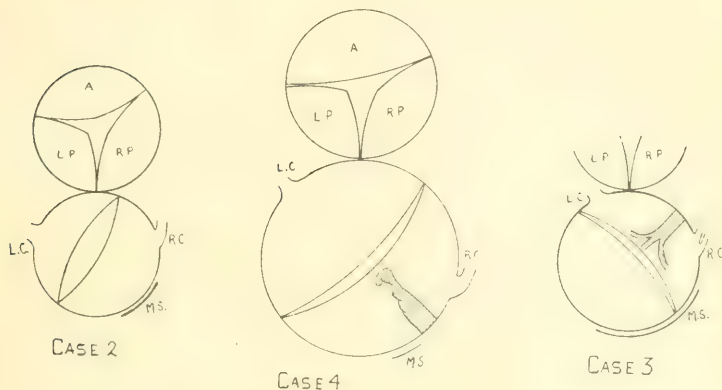


Fig. 4. Natural size diagrams of the basal arteries in three cases of bicuspid aortic valve. The drawings are to scale, though the margins of the valves are represented diagrammatically. The pulmonary artery lies above and the aorta below. One of the two cusps is partially subdivided in Cases 3 and 4. The subdividing ridge is drawn approximately to scale, but is represented in plan and not in section.

A. = anterior; *L.P.* and *R.P.* = left and right posterior cusps of pulmonary artery; *L.C.* and *R.C.* = left and right coronary arteries; *M.S.* shows the position and extent of the membranaceous septum relative to the cusps.

6 mm. of the cusp's margin. From the border of the sinus, the central ridge has a total length of 25 mm., a breadth of 4 mm., and a height of about 6 mm. in its centre; it reaches the insertion of the cusp 20 mm. from the start, proceeds on to the cusp, and falls short of the margin of the combined cusp by about 8 mm. Opposite the ridge the concave line of the cusp's attachment is broken by a triangular space, the floor of which is formed by a very small membranaceous septum. Both cusps have thickened margins, that representing the left anterior cusp especially. The noduli are not clearly distinguishable. That third of the attachment of the left anterior cusp, which forms commissure *A*, is extensively calcified, the calcareous deposit extending a few millimetres into the cusp itself, and an equal distance into the sinus. This deposit is seen in Fig. 16*d*: a calcareous deposit, similar in position and extent, is present in the attachment of the right anterior cusp at commissure *A*; the lower line of this bar of calcareous tissue is seen projecting from the ventricular surface of the valve at *f*. Similar deposits occur in the lines of attachment of the cusps forming commissure *C*, and one

of these is clearly shown at *E*. The serial transverse sections of the first 7 mm. of the ridge, representing commissure *B*, show central whorling of the medial elastic tissue. By the time the ridge increases in prominence this whorled area extends also into the superficial layers of the media, and the elastic elements are becoming sparser. A little lower the deep fibres of the media are thinning out, and the elastic elements are lost, superficially and deeply, at about the same level, namely, 13 mm. from the sinus border: there appears to be no distinct overlap, but the lines along which the elastic elements end is confused by degenerative changes in the ridge at this level. Above this level (8 mm. from its starting point) the ridge has increased in prominence, and here the first calcareous nodule is seen to lie in the most superficial layers of the whorled media. As the ridge is traced lower, hyaline and calcareous degeneration invades more and more deeply the substance of the ridge, which is now composed of the upward extension of the annulus fibrosus. The calcareous deposits lie very superficially at the sides of the ridge, and give rise to the chains of nodules previously described. Traced lower, the ridge broadens, but the same essential features are maintained; the subsidiary ridges are formed by the annulus, and show similar degenerative changes. At the level of the cusp's attachment the intermediate layer ("Zwischenschicht") is unusually developed and highly vascular. In the cusp itself the ridges are continued in the same form. The thickenings are confined to the fibrous layer of the valve, which extends continuously across the whole section, and is covered on the ventricular side by uninterrupted subendothelial and elastic layers, and by a central layer which is compressed opposite the main ridge. On the sinus side the ridge is sheathed by an unbroken elastic layer. The degenerative process has taken place on the sinus side of the fibrous layer of the cusp: a protective thickening of the sinus subendothelial layer has occurred.

In no part of the ridge or of the underlying tissues is there any sign of an inflammatory process.

Thus the cusps clearly illustrate congenital fusion, having been laid down, originally, in their present form. But the fused commissure has undergone degenerative changes, as have the remaining commissures in this specimen, and these degenerative changes are of the characteristic form described by Mönckeberg⁷⁵, and Dewitzky⁷¹, as constituting an advanced stage of annular sclerosis.

This calcification of commissure *B* is of particular interest, because it evidently occurs in those tissue elements which correspond to the annulus fibrosus and its normal extensions: thus linking up these structures in the malformed commissure, with corresponding structures in normal commissures. For it is the annulus, and its extension, which is the seat of this peculiar form of degenerative change, a process almost always present in some degree in patients of 40 years or over.

Part III. BICUSPID AORTIC VALVES IN INFECTIVE ENDOCARDITIS.

INFLAMMATORY UNION OF CUSPS.

When an adult patient dies of some intercurrent malady, and presents at autopsy two regularly concave aortic cusps like those illustrated by *Case 2*, there would be little hesitation in pronouncing the defect to be a congenital malformation on the macroscopic evidence alone. If, in a similar case, the autopsy displays two aortic cusps, one of which is divided by a ridge, as in *Case 3*, and there is little further abnormality of the valves, the opinion might be ventured again, on the macroscopic appearance of the specimen, that the defect originated congenitally: though such an opinion would be ventured upon a rather insecure basis. But if, in addition to a defect of these types, the same valves manifested signs of severe inflammatory disease, a decision as to the nature of the bicuspid deformity would necessarily become precarious in very many instances. When we first became interested in the contour of the aortic cusps in infective endocarditis, became impressed by the frequent association of bicuspid valves and began to investigate their nature, it soon became apparent that they might be explained in one of two ways. Either these valves were originally bicuspid, and had subsequently become the seat of an infective process, or they were bicuspid because they had been attacked by old or long standing inflammatory disease. After searching past records and attempting to collect from these such criteria as would satisfactorily enable us to recognise congenitally deformed valves, we came to the conclusion that the criteria then available were insufficient. We succeeded in finding reports of bicuspid valves themselves the seats of severe endocarditis, and often interpreted by the writers as primarily congenitally deformed valves. But the conclusion, though very possibly a correct one, was based upon evidence of an insufficiently convincing kind. A further consideration urged us to a more detailed study of such cases than had previously been undertaken, namely, that the cases with which we had to deal were cases of subacute or chronic infective endocarditis. For in this disease, as has become known in recent years, the formation of proliferating vegetations and healing may all occur in one and the same case, if not in one case at a given time. A combination of these processes, as we shall presently illustrate, renders it theoretically possible for normal valves to be converted into bicuspid valves of the types seen in the later stages of this disease: and until we could deny that subacute infective endocarditis is a process capable of complete healing— and we are not yet in a position to enter upon such a denial—the possibility had to be borne in mind that certain instances of bicuspid valve, found apart from active endocarditis, might be the healed products of such an infection long since cured. In this relation there is a fact, the full significance of which has not yet been grasped, namely, that subacute infective endocarditis may have a duration of at least two years. The questions which we regarded

as pertinent were these. If given valves were the seat of vegetations one or two years ago, what, to-day, represents those particular vegetations? Where is the scar tissue to which, so it might be judged from inflammatory lesions in other parts of the body, and from clots in the lumina of vessels, these vegetations must long ago have been reduced? Is it not possible that certain of the irregular partitions, standing in the place of commissures in infective endocarditis cases, really represent commissures ulcerated and subsequently healed and retracted? In seeming support of this possibility we observed several cases similar to those now used as illustrations.

Case 5. INFLAMMATORY PARTIAL FUSION OF R.A. AND P. CUSPS.

J. N., a carman, aged 20, was admitted to hospital on November the 17th, 1919, diagnosed subacute infective endocarditis. Except for an attack of rheumatic fever* at the age of 10, he had always been healthy, but had only served 3 months in France with a labour battalion when, in May, 1917, he began to suffer from breathlessness and giddiness on exertion. He continued his duty till May, 1918, and then, his symptoms progressing, he was admitted to hospital. Ultimately he was discharged from the army in June, 1918, on account of heart trouble; from that date until his admission his condition gradually became worse. On admission he showed signs of venous congestion with enlargement of the liver and congestion of the lungs. He was pale, the spleen was enlarged and his fingers were clubbed. The pulse was water-hammer in type, the heart moderately enlarged, and a to and fro murmur was audible at the base. The Wassermann reaction was negative and a blood culture yielded no growth. The red blood cells numbered 4,520,000 per c.mm., the hæmoglobin was 60 per cent. and the colour index 0.66. The leucocyte count was 4,300 per c.mm. The urine contained albumen, casts and blood. The temperature remained between 99° and 101° Fahr., the cardiac failure progressed and the patient finally died on January the 18th, 1920, from a cerebral embolus.

Pathological changes.

The lungs are cedematous and firmer than normal. The liver and kidneys are enlarged and infarcts are present in the spleen (weight 425 grammes) and kidneys. Sections of the kidney show numerous partially hyalinised glomeruli. The basal arteries of the brain are healthy, but one inch from its origin the left middle cerebral artery is blocked and distended with a grey clot half an inch long. The convolutions surrounding the lower part of the fissure of Sylvius show softening. The heart weighs 622 grammes; both ventricles are hypertrophied and dilated. The valves of the right side are normal. The mitral valve shows thickening of two or three of its chordæ, and a few small vegetations are found in the line of apposition of the cusps. The aorta is normal and the coronary vessels arise normally.

The aortic valve (Fig. 17) has been heavily attacked by disease. There are large and firm vegetations involving especially the margins of the right anterior and posterior cusps. These portions of the valve margins, which are free from vegetations, are thickened, smooth and rounded. The vegetations extend along the margins of the cusps to the top of commissure C, Commissure B is formed by a bar of tissue, 12 mm. long from the border of the sinus to the separation of the cusps: it is 2.5 mm. broad, and 5.5 mm. in depth at its maximum. Where the cusps separate at this commissure, a band of firm tissue unites them and partly fills the triangle (Fig. 17b). A small mass of vegetation sits on this bridge. The ridge of this commissure starts a considerable distance above the sinuses on the aortic wall (see Fig. 17). In serial sections,

* If rheumatic fever or chorea is not mentioned in the following case histories, it can be taken definitely that the patient had no knowledge of having suffered from it.

beginning at the border of the sinus, whorling is already conspicuous, and the elastic elements of the media are thinning out. Measuring from the border of the sinus, the whorling and thinning of the media continue for 2.5 mm.; at this level pure annulus fibrosus replaces the superficial layers of the media. This upward projection of the annulus replaces the media more and more until, 6.5 mm. from the top of the commissure, the elastic media disappears entirely from the mid-line. The general arrangement of the tissues at the top of the commissure is normal, that is to say, the annulus sends up a notable projection which overlaps the media superficially and forms the base from which the ridge springs. In sections, at various levels, the two original cusp edges can be identified, each showing a separate main fibrous layer, and each a separate sheathing by elastic layers. The fusion has occurred by an inflammatory union of the two ventricular subendothelial layers (as in Fig. 10); this central tissue of the ridge is highly vascularised and infiltrated. The tissue sheathing the two cusps and welding them into a single smooth edged ridge consists of connective tissue, of which the nuclei are numerous and somewhat flattened. As the sections are followed downwards the vascularity of the tissues increases, the connective tissue appears younger and more infiltrated, until finally the bridge (Fig. 17*b*) is reached. This bridge consists of connective tissue uniting the subendothelial layers of the adjoining cusps; it is relatively young, consisting of a fibrillar ground substance in which numerous flattened fibroblasts are seen; the nuclei of these fibroblasts are of long oval form. Commissure A consists of a smooth and rounded bar of tissue for the first 7 mm. of its course; its greatest breadth is 5 mm., its greatest depth 3.5 mm.. Below, it is the seat of ulceration, though the thickened remnants of the cusp margins are still easily traced laterally. The triangle is filled by a mass of sessile vegetations (*V*), which extend down the ventricular septum for some distance, and are guarded below by a crescent (*s*) of thickened endocardium. Serial sections were cut through this commissure and through the septal lesion below it. The medial elastic fibres are whorled, and are thinning out superficially, at the top of the commissure. They are gradually replaced by dense fibrous tissue, sparsely nucleated; this main fibrous mass lies superficially to the aortic media, the last ending 6 mm. below the top of the commissure; it is covered by a thick sheathing of younger connective tissue. There is little or no trace of the original layers of the cusps until the lower part of the ridge is reached. Here the evidences of active inflammation become abundant and vegetations are encountered in the sections. The vegetations on the septum, like those on the cusps, are mainly confined to the subendothelial layer, which is greatly thickened, and converted into granulation tissue of various ages. Fibroblasts and giant cells are numerous in the vegetations themselves; traced deeper, the connective tissue takes on the appearance of greater and greater age. In none of the sections of

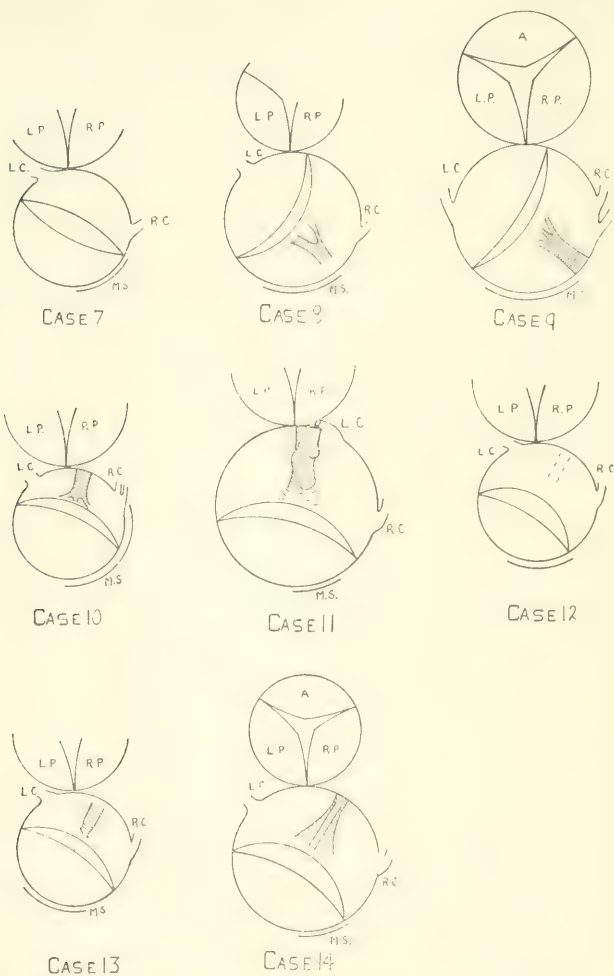


Fig. 5. Natural size diagrams to scale of the basal aortic valve in 7 cases of congenitally bicuspid aortic valve (Cases 7-13), and of 1 case in which fusion was probably inflammatory (Case 14). The reference letters are the same as in Fig. 4.

vegetation could organisms be found.* The crescent of thickened endocardium (s) consists of dense and rather sparsely nucleated fibrous tissue; the thickening is almost confined to the subendothelial layer.

These two disturbed commissures are frank examples of an inflammatory process, though whether that inflammatory process was purely contemporary with the endocarditis, found at death, may be open to question. There was, in this case, a previous history of rheumatic fever, and the fusion of the smooth portions of the commissures may have been of many years' standing. A final decision as to the date of such lesions cannot always be made in cases of subacute infective endocarditis; for the full course of the terminal disease is usually unknown, and the presence of active and widespread inflammatory changes at the time of death complicates the picture. Thus, the extent to which the older connective tissues represent healing of the infective endocarditis, must often remain in doubt†. The crescent of fibrous endocardium below the septal vegetations suggests a healed area, on which, perhaps, vegetations were once formed; very possible that has been the case, but it is a conclusion which we are not ready definitely to draw. That the bases of the vegetations were healing at the time of death is obvious, and this is compatible with the known duration of the malady. There is one lesion in this specimen which has special significance, namely, the bridge of tissue at the bottom of commissure *B*. This bridge is a new formation and its construction must definitely be regarded as contemporary with the last illness.

A similar bridge of new tissue, though of larger dimensions, has been found in another case of infective endocarditis (Table VI, *Case 16*), which we do not illustrate; the specimen was taken from a young man, whose infective endocarditis was known to have been of 15 months' duration. The commissure showed inflammatory fusion throughout its length, and was reduced to a rather thin *raphé* between the two adjoining cusps.

A third specimen, relevant to our present argument, is illustrated by the following case.

* In this instance and in subsequent case reports, this statement means that no collections of organisms could be found in sections stained by Gram's method, or by Murray's method (6th *Sc. Rep. of Imperial Cancer Research Fund*, 1919, 2nd method), although the vegetations were extensively explored.

† The same question has arisen in the case of many of the specimens subsequently to be described; usually it remains unsolved. It may be possible to express an opinion in many instances, but unmistakable evidence is not often to be obtained. We consequently avoid the question for the time being.

Case 6. INFLAMMATORY PARTIAL FUSION OF L.A. AND R.A. CUSPS.

E. R., a professional soldier, aged 35, was admitted to hospital on January the 22nd, 1919, diagnosed subacute infective endocarditis. Until 9 months before admission he had always been healthy except for an infection with syphilis in 1906, for which he had full treatment in the army. He then began to suffer from shortness of breath and palpitation on exertion with headaches and general pains, and these symptoms had since gradually become worse.

On admission the patient showed signs of general venous stasis with enlargement of the liver, oedema of the shins and congestion of the lungs. He was pale, with a brownish discoloration of the skin. The spleen was palpable and his fingers were slightly clubbed. The pulse was water-hammer in type, the heart enlarged. Systolic and diastolic murmurs were heard over both apex and base. The Wassermann reaction was negative, but a blood culture yielded a growth of a short chained streptococcus. Red blood cells numbered 4,200,000 per c.mm., hæmoglobin stood at 55 per cent. and the colour index was 0.65. The urine contained albumen but no blood. Later, he also complained of tender finger tips and of a red painful swelling in the right hypotenar eminence. A subungual hæmorrhage was noticed. His temperature remained between 99° and 100° Fahr., and his condition gradually became worse until he died of heart failure on May the 19th, 1919.

Pathological changes.

(Edema of the feet and legs) present. The organs are generally congested. The *spleen* is enlarged but not infarcted. The *left kidney* presents a small old infarct. The *heart* is a little enlarged. On the aortic flap of the *mitral valve* is a patch of sessile vegetation (Fig. 18, V) and a few small vegetations are found on the bases of the chordæ, which are slightly thickened; otherwise this valve is normal. These vegetations are well organised at their bases; they lie chiefly in the subendothelial layer of the valve, but the ventricular elastic layer has been broken at one place and the subjacent layers invaded. The coronary vessels arise normally. There is a small erosion near the orifice of the right coronary vessel, and this is surrounded by a few minute vegetations; otherwise the aorta is healthy.

The aortic valve is extensively diseased (Fig. 18), firm vegetations being collected mainly on its ventricular surfaces. One long pedunculated vegetation arises from the margin of the posterior cusp. Commissure A is represented by a solid bar of tissue 9 mm. long, 4 mm. broad at its widest, and 4.5 mm. in depth. It is smooth and rounded, and contains a little calcareous tissue. In the lower half of its course the lines of the cusps, largely eaten away, are easily traced. The triangle exists as a depression, but its outlet into the ventricle below is completely obstructed by a concave shelf of very firm vegetation, which stretches continuously from the middle of one cusp to the other. The apex of this mass of vegetation forms the most projecting portion of the valve. It is particularly to be noted that this shelf of vegetation replaces those portions of the adjacent cusps which have been destroyed, and that the line of the left anterior cusp margin may be traced in a continuous curve through the margin of the shelf into the margin of the right anterior cusp. In other words, since the loss of the commissural portions of the valve, a new valve margin has been formed of vegetation, which fills the gap and produces a single cusp out of the original two. This combined cusp is partly subdivided by the remnants of the commissure. No organisms were found in any of the sections taken from the vegetations in this specimen, although streptococci had been grown in the blood culture three months before death.

Now it is not supposed that this aortic valve as it stands would be mistaken for one of congenital origin; the appearances are still those of an inflammatory lesion; but the lesion, as the histology showed, was one progressing far towards healing, and the question naturally arises as to what would be the appearance of the valve at a later stage of healing, when the commissure itself might shrink further and the shelf of vegetations be more completely and smoothly organised. There can be little doubt that, macroscopically, it would closely resemble a congenitally bicuspid valve.

The microscopic examination of this commissure, however, reveals features distinctive from those of congenital origin. In transverse sections of the top of the commissure there is already whorling and thinning of the media superficially. The media is replaced superficially by annulus fibrosus 1 mm. from the beginning of the commissure, and wholly replaced by it 10 mm. from the beginning. In early sections remnants of the elastic layers of the fused cusps are distinct.

A central vertical section through the lower part of the commissure is shown in Fig. 13. In this section the projecting saddle of the fused commissure is seen above (*C*). It consists of old fissured fibrous tissue, covered with a thin and broken layer of elastic tissue, and by a thick and recent layer of young connective tissue, composing the subendothelial layer (*V.se.*). This young connective tissue forms the base of small healing vegetations (*V*). The fibrous tissue of this commissure connects up with annulus fibrosus (*A.F.*), which, as in normal commissures, lies superficial to the lower end of the aortic media (*A.M.*). In the lower part of the section the base of the false valve (*B.V.*) is seen in cross section. Centrally, this consists of firm fibrous tissue, vascular where it joins the endocardium. Its periphery is more nucleated, consisting of young but firm connective tissue. The vegetations, of which this projection formed the base, are not shown in the figure, having been cut away and examined separately. The connective tissue elements in the false valve, when traced further towards the margin of vegetation, present a gradual transition, fibroblasts becoming more and more numerous and succulent. The base of the false valve is penetrated by two strong leashes of elastic fibres (*e*), and is continued above and below into the ventricular subendothelial layer (*V.se.*) of the endocardium. The last is greatly thickened throughout, being converted into young but firm connective tissue, similar to that seen on the commissure and on the periphery of the false valve's base. The ventricular elastic layer (*V.e.*) runs as an intact layer throughout the section as far as the commissure. The whole of the tissue lying superficial to this elastic layer is a new formation, arising out of the endocarditis; the whole of it is to be regarded as representing organised or organising vegetations.

The points to emphasise in this specimen are several. The commissure has all the appearances of an inflammatory commissure, the upward projection of the annulus is extensive, and it overlaps the aortic media normally. The extent to which the vegetations have organised is notable; they have

healed to form a complete fibrous shelf crossing the triangle of the commissure and uniting the centres of the adjoining cusps, thus forming a false valve of considerable strength. The presence of elastic fibres, arranged in distinct layers in the false valve, is important. Supposing that in the case of a large cusp there is doubt as to whether it was originally laid down as such, or as to whether its central portion consists of new tissue formed as a shelf or bridge between the convexities of two adjoining cusps now thrown into one: the doubt would not be resolved by examining the central portion of the cusp for elastic elements, for they would be found in both circumstances. The question is to be solved by noticing the arrangement of the main elastic layers. The ventricular elastic layer is continued beneath the false valve as a continuous sheet, whereas, in the case of the true valve, its course alters as the cusp's attachment is reached: at this point the layer as a whole turns into the cusp to form one of its principal layers. The false cusp is purely a subendothelial appendage, the true cusp draws its layers from all layers of the endocardium, and from the underlying annulus fibrosus (Fig. 6).

In illustrating the microscopic features distinguishing cusps fused by inflammatory disease we use for the most part cases of subacute infective endocarditis: but attention has not been confined to such. For comparison, fused cusps from a variety of conditions, including those arising out of rheumatic endocarditis, some old standing and some more recent, have been examined. To generalise from our evidence, inflammatory fusions are recognised from the following criteria.

(a) In recent fusion, by the presence of the cellular elements of active inflammation and increased vascularity of the parts concerned. In old standing fusion by the presence of old fibrous tissue.

The presence of inflammatory elements does not serve, however, to distinguish inflammatory from congenital fusion, for commissures of the last kind may subsequently become inflamed.

(b) In inflammatory fusion, the architecture of the old commissure and cusp edges is usually clearly to be distinguished. That is so because the inflammation is mainly confined to the subendothelial layers, and leaves the remaining layers more or less undisturbed.

In the uppermost of serial sections through commissures fused by inflammation, the medial coat of the aorta continues unbroken behind the commissure (Fig. 7). The normal upward extension of the annulus lies superficially to this and into it the superficial elastic fibres of the media radiate at its sides. This arrangement is to be compared with that of Fig. 12, a congenital union in which the extension of the annulus lies behind the medial coat of the aorta. The inflammatory ridge consists of fibrous tissue in which remnants of the commencing cusp margins may or may not be visible. Even at such levels there often exists a conspicuous thickening of the subendothelial tissues which clothe the ridge

In sections taken at a lower level, and sometimes those taken at high levels (as in Fig. 7), unmistakable remnants of the original cusps are seen; they are outlined by their original elastic laminae (Fig. 10), and these may be intact from base to margin, but, usually, are more fragmentary. Each cusp has a more or less intact and separate main fibrous layer.

In the lowest sections, those which penetrate the ventricular cavity, the ventricular elastic layers of the fused cusps separate and become continuous on the two sides with the ventricular elastic layer of the endocardium. In inflammatory fusion of two cusps, the tissue adjoining the ventricular cavity at the base of the ridge is a new formation (Fig. 10, *Fus.*): it may, and usually does, contain newly formed elastic elements (*e*), but these do not constitute a distinct layer or one which is continuous with the elastic layer of the ventricular endocardium. Such an arrangement (Fig. 10) should be compared with that illustrated in Fig. 9. In this illustration of congenital fusion, the ventricular elastic layer continues unbroken across the ventricular surface of the combined cusps, and sends no projections forward into the ridge.

INSTANCES OF CONGENITAL FUSION.

Case 7. CONGENITAL FUSION OF L.A. AND R.A. CUSPS: SUBACUTE INFECTIVE ENDOCARDITIS.

J. M., a carman, aged 37, was admitted to hospital on February the 26th, 1920, diagnosed subacute infective endocarditis. Up to the autumn of 1919 he had always been healthy, and had served two and a half years in a labour corps with the army in France, being demobilised in September, 1919. He returned to his work as a carman and felt quite well till about the beginning of October, when he began to complain of shortness of breath and of pain over the heart. These symptoms gradually increased, and before admission he had been sweating profusely at nights and had suffered from a cough.

On admission he presented signs of venous stasis with enlargement of the liver and congestion of the lungs. He was pale, his fingers were clubbed and the spleen was enlarged. The pulse was water-hammer in type, and the heart moderately enlarged. A to-and-fro murmur was audible over the base of the heart and also at the apex, where, in addition, a diastolic thrill was palpable. The Wassermann reaction was positive, but no blood culture was made. The red blood cells numbered 4,500,000 per c.mm.; the haemoglobin was 66 per cent., and the colour index 0.73. The leucocyte count was 9,450 per c.mm.. The urine contained neither albumen nor blood. The temperature was for the most part normal with occasional rises to 99° or 100° Fahr.. The cardiac failure progressed with the development of ascites and oedema of the legs, and death took place on March the 12th, 1920.

Pathological changes.

Bilateral pleural effusion and oedematous lungs are found. The liver is enlarged and shows early nutmeg changes. Two small scars are present on its upper surface. The spleen weighs 550 grammes and contains one small recent infarct and a long depressed scar from old infarction. Both kidneys show several scars from old infarction and one anæmic infarct of more recent date; sections show very occasional completely hyalinised corpuscles and small areas of lymphocytic infiltration. The heart weighs 552 grammes. The ventricles are dilated and hypertrophied. The valves of the right heart are normal. The mitral valve presents one small vegetation on its aortic flap, but otherwise is quite normal.

The chief lesions are found in the aortic valve, and these are illustrated in Figs. 5 and 19. The right and left anterior cusps are thrown into one.

the coronary vessels arising from its margins. Below the mouth of the right coronary artery is the smooth opening of a sinus aneurism (*A*²), about 2 cm. in depth, containing laminated clot, and burrowing into the muscle of the infundibulum. Sections of the mouth and sac of this aneurism show firm old-standing fibrous tissue, diffusely inflamed. Below the orifice of the left coronary artery is a second aneurism (*A*¹) complex in outline, partly filled with clot, and projecting into the space between aorta and left auricular appendix. This aneurism has a thick whitish wall of firm tissue. The aortic cusps are of equal size (each measuring 32 mm.): they are large and irregular, and involved in almost all parts by thick and firm vegetations. Both cusps are perforated, the combined one by an extensive square aperture near its centre. This aperture is closed, marginally, by a coarse bar of vegetation. The perforation of the posterior cusp is smaller and near its centre. The limbs of commissure *B* are united for 5 mm.. The margin of the anterior cusp is replaced by a thick, smooth bar of shrunken tissue, which forms the posterior lip of the mouth of the sinus aneurism. Commissure *C* is completely involved by vegetations. In serial sections of all these cusps no organisms are found: the vegetations are for the most part in an advanced state of organisation. Thus the bar closing the square perforation consists mainly of fibrous tissue, coated by younger connective tissue, and eventually by débris on its surface. The remaining areas of vegetation are very similarly constituted, and little remains of the original valve substance. The specimen is evidently from a case of long continued endocarditis, much of which is in a relatively advanced stage of healing.

Looking into the combined sinus, a series of small fissures (*f*) is seen running vertically down the centre of the sinus. On the macroscopic evidence two interpretations of this specimen are possible. The cusps and portions of the sinus have been the seat of a long-standing inflammatory process, proceeding towards healing. The aneurisms and fissures may be regarded as the products of an ulcerative process, the latter representing the destroyed remnants of the original commissure, and the square aperture possibly represents the space originally separating the two cusps, bridged across at base and margin. The other view, which an extensive histological examination corroborates, is that the valve was originally bicuspid, and has subsequently become the seat of infective endocarditis. Transverse sections show that the elastic media is continuous throughout the sinus, reaching almost to the cusp's attachment throughout its extent. The bridge of tissue, guarding the square aperture on the side of the cusp's attachment, contains the perfect layers of the normal cusp, and these layers are continuous with the ventricular endocardium below and the aortic coverings above. The sweep of the cusp's attachment is uninterruptedly concave. The fissures do not represent a commissure: the deepest laminae of the elastic media run unbrokenly beneath most of them, though the layers are fractured by the fissures in places to three parts the total thickness, and in one place completely. They are lined, for the most part, by a thick layer of quite young connective

tissue, compact and serial layers of young fibroblasts, or by young granulation tissue. Beneath the fissures the adventitia shows perivascular infiltration.

The specimen has a similar origin to that of *Case 2*, but, in this instance, the right and left anterior cusps are combined, and the valve has become the seat of an infective process.

Case 8. CONGENITAL PARTIAL FUSION OF R.A. AND P. CUSPS: SUBACUTE INFECTIVE ENDOCARDITIS.

J. D., a packing case maker, aged 40, was admitted to hospital on April the 19th, 1920, diagnosed subacute infective endocarditis. Previous to enlisting in 1915 he had always been healthy, and he served abroad till April, 1917, when he was admitted to hospital for trench fever. Subsequently he returned to his unit, but found himself unable to continue duty because of shortness of breath and fatigue on exertion. He was then examined by a medical board and found to be suffering from heart disease, on which account he remained on light duty till demobilised in June, 1919. In February, 1920, the symptoms became worse and he became troubled by a persistent cough.

On admission he showed signs of advanced cardiac failure with cyanosis, enlargement of the liver, ascites and congestion of the lungs. The spleen was palpable; there was conspicuous clubbing of the fingers, and there were a few petechial hæmorrhages in the skin of the neck. The pulse was water-hammer in type and the heart moderately enlarged. A loud to and fro murmur was audible over the base of the heart, and also at the apex. The Wassermann reaction was negative, but no blood culture was made. The red blood cells numbered 4,700,000 per c.mm., the hæmoglobin percentage was 72 and the colour index 0.76. The leucocyte count was 13,000 per c.mm.. The temperature remained between 99° and 100° Fahr., with occasional remissions, and death occurred on May the 22nd, 1920, from increasing heart failure.

Pathological changes.

Both lungs are congested and oedematous. The right pleural cavity is totally obliterated and in the left 2 pints of clear fluid are found. The liver is congested and shows early fatty change. The spleen weighs 254 grammes; it is not infarcted. Both kidneys are scarred by old infarcts and their capsules thickened. In one kidney a group of completely, but no partially, hyalinised corpuscles are seen. The heart weighs 466 grammes; the hypertrophy is in the left ventricle; neither ventricle shows much dilatation postmortem. The valves of the right ventricle are normal; the mitral valve is normal with the exception of a single smooth vegetation the size of a pea, on the posterior cusp and two small patches of sessile vegetations at the base of the aortic cusp. The aorta is normal and the coronary arteries arise normally.

The aortic valve is severely diseased (see Figs. 5 and 20). Commissure A is involved by extensive vegetations which invade the adjoining cusp margins. The commissure itself is greatly thickened and completely calcified, and the vegetations are also undergoing calcification. Before the aorta was opened, the masses of vegetation on either side of the commissure were firmly united to each other, leaving a gap on the sinus side. Below this gap, and in the triangle itself, the endocardium is thickened in patches, some of which are whitish in colour, others of which are yellow, owing to the presence of many polymorphonuclear leucocytes lying in the necrosed muscle, which is laid bare. There are also several areas of minute vegetations in this region. The vegetations on the valve are all firm, and no organisms are to be found in sections cut of them. The right anterior and posterior cusps are thrown into one: these cusps measure 26 and 20.5 mm. respectively: the left cusp measures 28 mm.. The cusp edges at commissure C are much thickened.

The commissure itself is fused for a distance of 4 mm., and the ridge has a breadth of 6 mm.. The fusion is of the inflammatory type, remnants of the cusp's elastic layers being encountered in the upper transverse sections, but being deeply embedded in young and vascular subendothelial tissues. Whorling of the media is seen at the top of this short ridge and the annulus appears almost immediately. The deep elastic lamina of the media are continued for approximately 9 mm., or 5 mm. beyond the end of the ridge. Both media and adventitia are infiltrated and vascular, the vessels showing obliterative endarteritis.

Commissure *B* is represented by a smooth, low ridge, descending 10 mm. into the sinus, having a maximum breadth of 3 mm. and a depth of $\frac{1}{2}$ to 1 mm.. Before reaching the line of the valve's attachment it breaks into two limbs, and between these two the upper part of the membranaceous septum is enclosed on the sinus side of the valve. The two limbs end shortly after reaching the valve's attachment. Serial transverse sections of this ridge show elastic tissue of the media extending down 10 mm., that is to say, as far as the subdivision. The first serial sections of this ridge show slight whorling of the elastic tissue in the aortic media. As the sections are traced down the whorling increases, especially centrally, many fibres appearing punctate in cross section; and the elastic elements become sparser, being first completely lost in the deeper layers of the ridge, when the pure fibrous tissue of the annulus appears. This junction occurs 7.5 mm. from the beginning of the ridge, and is represented in Fig. 12. Elastic elements are continued, superficially, in the ridge for another 2.5 mm., ending where the main ridge ends. Here the ridge becomes constituted of thickened annulus only, the tissues of the annulus being similarly whorled, and the subsidiary ridges at the bifurcation are continued in this form.

In the lower sections the ridge is sheathed by a well-developed sinus elastic layer, and by a somewhat thickened subendothelial layer. There is little or no sign of active inflammation in the ridge itself, and no sign of old inflammation, but in the adventitia beneath and to the sides of it there is a little perivascular infiltration, and the vessels, as in many of these cases, often show obliterative endarteritis. In transverse sections of the base of the combined cusp, immediately beneath the divided ridge, the usual layers are seen extending, without break, across the section. These layers may be identified readily with the normal layers of the cusp: the ventricular subendothelial layer is, however, thickened (by well-nucleated connective tissue, penetrated by elastic fibres), and the fibrous layer of the cusp presents some calcareous deposits in the termination of the ridge (annular sclerosis). As the thickened subendothelial layer is traced in subsequent sections towards the cusp margin, it thickens more, becomes infiltrated and vascular, and contains younger fibroblasts, until the actual vegetations are reached.

This commissure, undoubtedly a malformation, closely resembles that described in *Case 3*, though in the latter, it was the right and left anterior

cusps which were united, while in the present case it is the right anterior and posterior cusps.

Case 9. PARTIAL CONGENITAL FUSION OF R.A. AND P. CUSPS; SUBACUTE INFECTIVE ENDOCARDITIS.

E. U., a motor driver, aged 33, was admitted to hospital on the October 17th, 1922, diagnosed malignant endocarditis. He served in the army from 1915 to 1919, and in 1917 had an attack of trench fever. In 1919 he had influenza, followed by pneumonia, but apart from these he had enjoyed good health till 9 weeks before admission, when he began to suffer from shortness of breath and cough. From the same date he had lost flesh and for a week had been troubled by a persistent cough.

On admission he showed no definite signs of venous stasis. He was sallow, and his fingers were very clubbed. The heart was enlarged and the pulse of water-hammer type. A to and fro murmur was audible at the aortic cartilage and also at the apex. The Wassermann reaction was negative and a blood culture gave no growth. Red blood cells numbered 2,960,000 per c.mm., the haemoglobin percentage was 50 and the colour index 0.8. The leucocytes count was 4,300 per c.mm.. The urine contained albumen and blood. The temperature remained between 99° and 100° Fahr., full signs of cardiac failure soon developed and the spleen was palpable. Death occurred on December the 14th from cardiac failure.

Pathological changes.

Edema of the feet and legs is present. There are effusions in all the serous cavities and the organs generally are congested. The spleen weighs 650 grammes and shows several infarcts. Both kidneys are enlarged, their capsules slightly thickened and their surfaces mottled; sections show early interstitial nephritis, many completely and a few partially hyalinised corpuscles. The heart weighs 495 grammes. The ventricles are both dilated and hypertrophied, the right more particularly. The valves of the right ventricle present no significant changes. The *tricuspid* valve is but little diseased. A few small vegetations weld together the tertiary chordæ of the posterior cusp. The aortic cusp is similarly affected, and several chordæ of this cusp show small vegetations running down almost to the papillary muscles. Below commissure *C* on the aortic cusp (Fig. 21) is a diseased area; the upper portion of this is rough, owing to the presence of granular vegetations, the lower portion is an area of thickening, smooth and glistening on its surface. The *aorta* is normal, but for a few small and scattered atheromatous patches. The coronary vessels arise normally, the right by means of two separate mouths.

The margins of the *aortic cusps* are involved by vegetations (Figs. 5 and 21), except in the immediate neighbourhood of the commissures; these vegetations extend on to both aortic and ventricular surfaces of the cusps, and have perforated the left anterior cusp. The vegetations are firmly attached, and many of them advancedly calcareous. Near commissure *C*, in the posterior cusp, is the mouth of a shallow aneurism of the sinus (*a*). Below commissure *A* are several yellowish white thickenings of the septal endocardium. The origins of the cusps are unusually separated at commissures *A* and *C*, and one cusp margin (at commissure *C*) is fenestrated. The margins of the cusps at the commissures are a little thickened. Commissure *B* is represented by a long ridge, and the right anterior and posterior cusps are fused into one (Fig. 5). The ridge extends downwards for 9 mm., as a single and smooth elevation, having a breadth of 3½ mm., and a maximal height of 2 mm.. It terminates by subdividing into three small ridges, one continuing the main ridge, the other two diverging. The latter end at the attachment of the valve, the central ridge proceeds a few millimetres on to the

cuspid, and ends in thickened tissue at the base of the vegetations. The end of the media of the aorta is distinctly visible in the fresh specimen; it terminates where the ridge subdivides. The left anterior cusp measures 34 mm., the right anterior 25 mm., and the posterior 22 mm.. The sweep of the combined cusp's attachment is broken by a very distinct triangle on the ventricular side. Serial sections of this commissure show slight whorling at the top of the ridge. As the sections are traced downwards, the whorling increases, especially centrally, and many more elastic fibres are seen in cross section. Lower still the laminated appearance of the ridge is almost entirely replaced, centrally and superficially, by the punctate cross sections of elastic fibres. This punctate condition persists, but the fibres become sparser and sparser until the pure fibrous tissue of the annulus is encountered 7.5 mm. below the top of the ridge, a point a little above its subdivision. At this point the deep part of the ridge still shows a few elastic laminae crossing it, but these in turn disappear 0.5 mm. lower down. Beyond this level, the ridge and its subdivided continuation, consist of pure annulus only. There is little or no sign of inflammation beyond vascular congestion and slight perivascular lymphocytic infiltration in the ridge and in the neighbouring sinus wall. Transverse sections of the base of the combined cusp show the usual layers running across the section without break. The ridges on the valve are seen to lie in the fibrous layer, and to be formed by the continuation of the subdivided ridge of the commissure. Passing out on the cusp, the layers, particularly on the ventricular side, become disturbed by the presence of new connective tissue and lymphocytes, and, as the area of vegetation is reached, the connective tissue becomes younger, and the lymphocytes more numerous. There are small scattered deposits of calcified material in the fibrous layer in the upper part of the valve, and others, more numerous and larger, are found in the vegetations themselves.

The defect in the usual upward prolongation of the annulus at the commissure, and the perfect stratification of the combined cusps, proclaim the specimen to be a congenital malformation.

Case 10. CONGENITAL PARTIAL FUSION OF L.A. AND R.A. CUSPS: SUBACUTE INFECTIVE ENDOCARDITIS.

A.H., a clerk, aged 28, was admitted to hospital on March the 23rd, 1920, diagnosed subacute infective endocarditis. He enlisted in 1914, having previously been healthy, and served for three years with an infantry battalion in France. Except for an attack of influenza in 1915, and being slightly gassed in 1917, he remained well and was demobilised as fit in February, 1919. In December, 1919, he began to complain of pain over the heart, general malaise, cough and breathlessness. He also noticed that he was getting thinner.

On admission there were signs of venous congestion with enlargement of the liver. He was pale, somewhat wasted, his fingers were clubbed and the spleen was palpable. On the right forearm below the elbow was a small expansile tumour, three-quarters of an inch in diameter, apparently an aneurism of the radial artery. The pulse was of water-hammer type and the heart slightly enlarged. A to and fro murmur was audible at the base and also at the apex. The Wassermann reaction was positive, but no blood culture was made. The red blood cells numbered 4,050,000 per c.mm., hæmoglobin being 70 per cent., and the colour index 0.86. The white cells were 9,000 per c.mm.. The temperature remained about 100° Fahr. with occasional intermissions, and the cardiac failure increased. Death took place on June the 7th, 1920.

Pathological changes.

Both lungs are edematous and the right contains several hemorrhagic infarcts. Bilateral hydrothorax and ascites are also present. The *liver* is enlarged and congested, the *spleen* weighs 382 grammes and contains old and recent infarcts, as do the *kidneys*. There is a small mycotic aneurism on the upper part of the right radial artery. The *heart* weighs 523 grammes, there is slight hypertrophy and dilatation of both ventricles. The valves of the right ventricle are normal. The *mitral* valve has numerous small vegetations upon its ventricular aspect; these mat together the chordæ tendineæ at their insertions, and in places are found a little way down the chordæ. The auricular surface of the valve is normal. The *aorta* (Fig. 22) shows a few small and scattered atheromatous patches at its base. The coronary arteries arise normally. Immediately to right and left of commissure *A* and a little above its beginning are two stellate fissures in the aortic wall (Fig. 22, *f*). Sections of the left hand fissure shows it penetrating the media almost completely. The elastic laminae are broken short at the edges of the fissures, their ends being covered with a thin layer of homogeneous staining material. One edge of the fissure is lined in part by layers of young fibroblasts. The surrounding elastic laminae are infiltrated by small collections of lymphocytes, extending for some distance. The adventitia deep to the fissure is likewise infiltrated, and its vessels in this region show advanced proliferation of their intimal lining, up to actual obliteration of their lumina. The right hand fissure just penetrates the media, but is otherwise similar to the first.

The *aortic* valve (Figs. 5 and 22) has large, flat vegetations attached to its margins and ventricular surface and the posterior cusp is torn. The vegetations are firmly attached, and tough. They do not invade the commissures to any great extent: here the valve edge is thickened but smooth. In sections of the vegetations no organisms are discovered. The end of the long pendulous vegetation, when tilted upwards, comes into apposition with the two small aortic fissures (*f*). Commissure *A* is represented by a smooth ridge, having a length of 17.5 mm., and extending a few millimetres on to the cusp; its breadth is 3 mm., and its greatest depth 2.5 mm.. Just before reaching the cusp's attachment it sends off two subsidiary lateral ridges (see Fig. 5) which can be traced about 7 mm. over the cusps. Opposite this ridge on the ventricular side is a small angular break in the sweep of the combined cusp. Thus the left and right anterior cusps are thrown into one; they measure 15 and 17.5 mm. respectively, and the posterior cusp measures 30.5 mm.. Whorling is present in the top transverse sections of the ridge. It is continued downwards for 5 mm.; the elastic elements then begin to become sparser. They disappear gradually in all the layers of the ridge simultaneously, and the last trace of them is seen in sections taken 9 mm. from the top of the ridge.

The edges of the aortic media do not overlap the annulus; the junction is a straight one. Here the pure tissues of the annulus begin. The lower part of the main ridge, and the subsidiary ridges, are constituted by projections of the annulus, and of the fibrous layer of the cusp. When the cusp is reached its layers are seen to run continuously across the sections. There are no signs of active inflammation in the ridge or underlying tissues in its course through the sinus; increased vascularity of the tissues and a little infiltration begins at the level of the cusp's attachment.

These appearances characterise the deformity as being a congenital malformation.

Case 11. CONGENITAL PARTIAL FUSION OF *L. A.* AND *R. A.* CUSPS; SUBACUTE INFECTIVE ENDOCARDITIS AND CALCIFICATION OF THE VALVE.

B. R., a clerk aged 30, came under observation in May, 1920. He had experienced three attacks of rheumatic fever (the last in 1910), but enlisted in 1917 and did full duty abroad till January, 1918, when he developed nephritis. At that time he also complained of shortness of breath and fatigue on exertion, and was ultimately discharged from the army in July, 1918. His condition remained the same until May, 1920.

On admission he showed no signs of venous congestion, but his exercise tolerance was poor. He was pale, the spleen was palpable and his fingers conspicuously clubbed. The pulse was of water-hammer type and the heart considerably enlarged. Systolic and diastolic murmurs were audible over both apex and base. The urine contained a heavy cloud of albumen.

On July the 15th he was admitted to hospital with full signs of advanced cardiac failure. He was too ill to admit of further examination, and died two days later.

Pathological changes.

Both *lungs* are congested. The right lung is totally adherent to the pleura and in the adhesions at the base is a mortar-like mass 2 inches wide, surrounded by fibrous tissue. The lung tissue contains scattered caseous nodules. There is slight *ascites*. The *liver* and *spleen* are enlarged and congested. The former shows nutmeg changes and the latter contains one small pale infarct. Both *kidneys* show slight mottling of the surface. The *heart* weighs 434 grammes. Both ventricles are considerably dilated and hypertrophied. The valves of the right heart are normal. The posterior cusp of the *mitral* valve is normal; the *aortic* cusp has a large patch of sessile vegetations upon it and these extend up as far as the aortic valve, and downwards to involve the insertions of the chordæ. Numerous small vegetations are found on the chordæ at a lower level. The ventricular septum is normal. The *aorta* is normal. The coronary vessels both arise from the right anterior cusp.

The *aortic* valve (Figs. 5 and 23) is heavily involved along its edges by large firm vegetations, some of which are pendulous. The vegetations have spread a considerable distance on both the sinus and ventricular surfaces of the cusps and the posterior cusp has a ragged aperture in its centre. Some of the vegetations are heavily impregnated with lime salts. Commissure *C* is involved throughout its length by vegetations, which are united to each other. There are a few minute vegetations in the wall of the posterior sinus. One cusp margin of commissure *B* is invaded by vegetations, the other shows thickening. None of the vegetations in this specimen show organisms in their sections. Commissure *A* is reduced to a low ridge, and the right and left anterior cusps are fused together. The left and right anterior cusps measure 21.5 and 24.5 mm. respectively; the posterior cusp measures 28 mm.. The line of attachment of the combined cusp is seen, from the ventricular side, to be broken by a small triangle opposite the ridge. The ridge of commissure *A* extends down the wall of the sinus for 15 mm.; its breadth is 4 mm. and greatest depth 5 mm.. It is continued in the same form on the combined cusp until it is lost in calcareous vegetations in the margin. The ridge is nodular, rough and hard, obviously containing much calcareous tissue. The bases of all cusps show an early grade of annular sclerosis.

The serial transverse sections through the upper part of the ridge show the usual whorling of the elastic elements, many fibres being cut in cross section. Calcareous tissue first appears as a nodule 4.5 mm. from the top of the ridge, and this nodule is situated in the superficial layers of the whorled elastic tissue. A little further down the medial elastic fibres begin to become

sparser. As the sections are traced lower still, calcareous nodules more and more replace the whorled tissue of the ridge; 7 mm. from the top of the ridge the elastic elements of the media are lost superficially. They disappear deeply at a point about 8 mm. down the ridge from its beginning. At this level the calcareous deposits begin to be surrounded and pervaded by granulation tissue; but there is little or no sign of inflammation in the ridge apart from this, and the underlying adventitia shows very little infiltration. In lower sections the ridge is composed of calcified annulus fibrosus. Thus there is probably a slight overlap between annulus and media in the usual direction, though the architecture is much disturbed by the calcareous deposits.

Down to the level of the cusp's attachment, and beyond it, the ridge is still continued in the same form, the base of the cusp is very vascular, and, as the sections are followed into the cusp, lymphocytic and polymorphonuclear infiltration increases more and more until it becomes intense; but the ridge lies exclusively on the sinus side of the cusp, and is covered on its ventricular side by unbroken ventricular and subendothelial elastic layers, both of which, but especially the former, become thickened by new connective tissue elements as the body of the cusp is approached. The fibrous layer of the cusp is also traced from side to side as a continuous layer, though in the neighbourhood of the ridge it is deeply involved by calcareous matter, starting on the sinus side. A broken sinus elastic layer is traceable over the greater part of the ridge, where it lies on the cusp; it is covered in turn by a very thickened sinus subendothelial layer, the thickening being due to new connective tissue elements, and eventually to vegetations. The fusion is quite clearly of the congenital type, but, in the cusp, the line of fusion has been involved by the inflammatory and degenerative processes, and in the sinus, by more purely degenerative processes.

The degenerative process in the sinus portion of the ridge has probably the same pathological origin as has annular sclerosis, such as was found and fully described in *Case 4*. This is evidenced by the first appearance of calcareous nodules in the superficial layers of the annulus, and on the sinus side of the fibrous layer of the valve.

Case 12. CONGENITAL FUSION OF *L.A.* AND *R.A.* CUSPS: SUBACUTE INFECTIVE ENDOCARDITIS.

J. M., aged 32, a concert artiste, was admitted to hospital on November the 27th, 1919, suffering from subacute infective endocarditis. He enlisted in 1915, having previously been healthy except for occasional sore throats, which ceased after tonsillectomy in 1908. He served in France and remained well till June, 1918, when he had a sudden "stroke" with numbness and pins and needles down the right side. These sensations gradually passed off, but he felt thoroughly run down, and later complained of tenderness under the finger nails. Ultimately he was sent to England and was demobilised in January, 1919. After that date he noticed a throbbing in his neck and suffered from intermittent pains and swelling of the calves of the legs. He became irritable and was breathless on the slightest exertion.

On admission the patient showed signs of venous stasis with enlargement of the liver. He was pale, the spleen was palpable and soft, his fingers were clubbed and Osler's nodes were present.

There was an acutely tender swelling of the calf of the right leg. The pulse was water-hammer in type and the heart was moderately enlarged. A to and fro murmur was audible all over the precordium but most clearly at the base, and a diastolic thrill was palpable at the apex. The Wassermann reaction was negative and a blood culture yielded no growth. Red blood corpuscles were 4,100,000 per c.mm., the hæmoglobin being 70 per cent., and the colour index 0.85. There was a leucocyte count of 18,000 per c.mm.. The patient remained in much the same condition with a temperature averaging between 99° and 100° Fahr., until, after several paroxysms of dyspnoea and vomiting, he died on January the 8th, 1920.

Pathological changes.

Bilateral hydrothorax and congested lungs are present. The mucous membrane of *stomach and intestines* is congested. The *liver* is enlarged and congested; the *spleen* weighs 269 grammes; it is not infarcted. Both *kidneys* are firmer than normal, and sections show small areas of lymphocytic infiltration. The *right posterior tibial artery* is closed by a partly organised clot at a point about midway between knee and ankle. The *heart* weighs 665 grammes, both sides being hypertrophied and dilated. The valves of the right ventricle are normal. The aortic flap of the *mitral valve* has a few sessile vegetations upon it and a more extensive patch beneath the aortic valve. There are many vegetations on the chordæ, occupying, as they frequently do, almost exclusively the points where the chordæ subdivide. The posterior cusp of the valve is less affected. The *aorta* above the sinuses is normal.

The *aortic valve* (Figs. 5 and 24) is heavily involved along practically the whole of its margins. These are encased in thick, rough, but firm, vegetations. The posterior cusp has been perforated, the margins of the perforation, especially the lower, being smooth. Commissure *B* has been destroyed almost completely, though its original lines are detected as low ridges. The triangle is filled with small vegetations, which extend down on to the septum. A long pendulous vegetation hangs down from this region into the ventricle (before the photograph was taken the aortic flap of the mitral valve had been cut away). These vegetations are surrounded by an area of thickened subendothelial tissue, which the microscope proclaims to be recent. In the posterior sinus a fissure is seen near the cusp's attachment. The right and left anterior cusps are thrown into one; they measure 20 and 21 mm. respectively; the posterior cusp measures 23 mm.. The coronary arteries arise from this combined cusp, and the mouths of both are greatly eroded, the left one having numerous fresh vegetations around it. The intima is replaced by masses of young connective tissue cells, standing alone, or at the bases of small thrombi. The elastic laminae of the media are much disturbed and infiltrated with lymphocytes, and in places broken off short. Neither these nor the valvular and septal vegetations contain visible organisms. Much of the rest of the sinus is eroded or occupied by small vegetations. The remains of the commissure (commissure *A*) are seen as a vertical line of small elevations in the sinus, though this is continued as a more distinct ridge on the cusp itself. Serial transverse sections of this region show the remnants of the commissure to extend for 17 mm. from the border of the sinus to the cusp's attachment. The elastic laminae of the media are whorled from the start, and this whorling continues down for 3 mm., when, in addition, the elastic elements begin to become sparser in the deeper layers of the media. This thinning continues until the pure annulus appears 6 mm. below the border of the sinus. Superficially the

elastic elements continue 4 mm. further, and the ridge then consists of projecting annulus only; it is traced as a broken structure on to the cusp, where it is formed by a thickening of the fibrous layer of the cusp. This fibrous layer runs unbroken throughout the section of the combined cusps, and is sheathed by a complete and unbroken endocardial layer, and by similar sinus layers.

Thus the fusion is typical of the congenital malformation, but the ridge is obscured by subsequent inflammation. The sections show frequent areas of perivascular infiltration in adventitia and media, the small arteries being often obliterated. Here and there the media is disturbed superficially and, at this point, the intimal tissue is converted into small masses of granulation tissue. Similar inflammatory disturbances are seen scattered along the whole length of the ridge.

Case 13. CONGENITAL FUSION OF L.A. AND R.A. CUSPS; SUBACUTE INFECTIVE ENDOCARDITIS.

F. M., a clerk, aged 24, was admitted to hospital on 25th October, 1919, diagnosed subacute infective endocarditis. He had always been healthy, and enlisted in 1914, serving two-and-a-half years in the line. In May, 1917, he had an attack of pyrexia of unknown origin, for which he was in hospital for 16 days. He continued in the army until his discharge in March, 1919. Breathlessness, palpitation and giddiness on exertion then began to trouble him, and he also noticed that his finger tips were sometimes tender without apparent cause. His symptoms gradually became worse.

On admission he presented signs of venous congestion, had a yellowish tinge, his fingers were clubbed, and the spleen was enlarged and soft. There was a subungual hemorrhage in the right thumb. The pulse was water hammer in type and the heart moderately enlarged. A diastolic murmur was audible at the base and at the apex a confused rumble throughout the cardiac cycle could be heard. The red blood cells numbered 4,900,000 per c.mm., the hæmoglobin percentage was 60, and the colour index 0.6. The leucocytes were 6,300 per c.mm.. A blood culture yielded no growth. The urine contained albumen and blood. The further course was rapidly increasing heart failure with nocturnal paroxysms of dyspnoea and vomiting. The temperature remained between 99° and 100° Fahr., and the patient ultimately collapsed and died on December the 9th, 1919.

Pathological changes.

Fluid is present in both pleural cavities and both lungs are congested and fibrotic. Moderate ascites is present and the mucous membrane of stomach and intestines is congested. The liver is congested and shows early nutmeg change. There are old infarcts in both kidneys and in the spleen, the latter weighing 297 grammes. The heart weighs 609 grammes, the ventricles being hypertrophied and dilated. The foramen ovale is patent. The valves of the right heart are normal. The posterior flap of the mitral valve is normal; its aortic flap presents extensive vegetations on its ventricular surface, and three small aneurisms (not displayed in Fig. 25) project towards the auricular cavity. The chordæ tendineæ of this cusp are invaded by many small vegetations and the smaller chordæ are bound together. The aortic wall is normal, the coronary arteries arise normally.

The greater part of the margin and body of the posterior cusp of the aortic valve (Figs. 5 and 25) is converted into densely calcareous vegetations. The left and right anterior cusps are united into a single pendulous structure,

involved by firm vegetations almost to the line of its attachment. No organisms were found in sections of these vegetations. Commissure *C* is not adherent; here the valve margins, though thickened, are free from vegetation. Commissure *B* is largely destroyed, though the two smooth remnants of the thickened and retracted cusps are clearly visible. The ridge, before its subdivision, is 8 mm. long. In the top transverse sections the superficial elastic laminae of the media are already replaced by fibrous annulus; the media is continued deep to the annulus for a distance of 7 mm., the length of the ridge. Outlines of the original cusps, their elastic layers, are clear from a point 5 mm., down the ridge, and onwards. There is widespread infiltration and increased vascularity of the ridge and underlying tissues. Endarteritis obliterans is well displayed by the adventitial vessels.

Below this commissure the septal endocardium has been invaded by minute vegetations, surrounded by an area of thickened endocardium, which, at its lowest point, is thrown into a short overhanging fold. Of commissure *A* there are but traces; an irregular ridge ends in a little nodule, and a slight ridge is then continued into the thickened cusp. These remnants have a length of 11 mm. to the cusp, and the maximal depth is 1 mm.. The base of the cusp where the ridge joins it is less translucent than at its sides, and a band of thickening appears to continue a few millimetres into the cusp. On the ventricular side the line of the cusp's attachment shows a small but recognisable break opposite the ridge. The left and right cusps measure 17 and 18 mm. respectively, the posterior measures 28 mm.. In the serial transverse sections the medial elastic laminae are whorled at the top of the ridge; they soon begin to become sparser in the deeper layers of the ridge, and pure annulus is encountered at the level of the little nodule 5 mm. from the top of the ridge. Superficially the media overlaps the annulus for a further distance of 3 mm.. The little nodule consists of young fibrous tissue, lying superficially to the aortic media. Below the nodule the ridge consists of a thickening of the annulus, and is continued as such. The adventitia underlying this ridge, and the ridge itself, shows sparse infiltration. The infiltration of the media is confined to the level of the nodule, and below it. In the lowest sections the base of the combined cusp is cut across; it presents the usual layers passing continuously across the section; both subendothelial layers (sinus and ventricular) are thickened by connective tissue elements, which have been laid down in them.

Thus, this commissure, although it might have been regarded as eroded and healed on macroscopic examination, proves, when examined histologically, to be a congenital malformation.

The last seven cases (*Cases* 7-13) all illustrate bicuspid aortic valves of congenital origin. In the same series of specimens is an example of a somewhat different kind. It is shown in Figs. 5 and 26.

Case 14. FUSION (PROBABLY INFLAMMATORY) OF THE L.A. AND R.A. CUSPS :
SUBACUTE INFECTIVE ENDOCARDITIS.

G. F., a serving soldier, aged 32, was admitted to hospital on March the 15th, 1919, as a case of infective endocarditis. Except for an attack of rheumatic fever at the age of 13, he had always been healthy. He enlisted in 1916, served in France, and remained well until June, 1917, when he had a slight attack of pyrexia of unknown origin. A year later he again developed pyrexia with cough and expectoration. In November, 1918, he complained of feeling ill with sleeplessness, loss of appetite and severe abdominal pain, and later the pyrexia, cough and expectoration returned.

On admission he showed no signs of venous congestion. He was pale, wasted, and had a yellowish-brown complexion. The spleen was palpable, but the fingers were not clubbed. The pulse was of water-hammer type and the heart moderately enlarged. A to and fro murmur was heard at the base and a diastolic rumble at the apex, together with a systolic murmur and thrill. The Wassermann reaction was negative and a blood culture yielded no growth. No tubercle bacilli were found in the sputum. The red blood cells numbered 4,000,000 per c.mm. The urine contained albumen but no blood. The temperature remained about 99° Fahr., and on April the 12th he developed a left hemiplegia. This persisted until he died on May the 9th, after having attacks of rectal hæmorrhage for several days.

Pathological changes.

The right lung is normal, but the left is generally adherent to the parietal pleura and at the apex is shrunken, and contains a few old tuberculous nodules. The liver shows fatty degeneration. The spleen is enlarged, adherent to the liver, and contains three recent infarcts. The kidneys are deeply injected, show fatty degeneration, but are not infarcted. The ileum is deeply injected for about one foot of its length where an embolus of a mesenteric artery is found. The brain shows flattening of the convolutions of the right side and the right ventricle is full of recently clotted blood. There is maceration of the brain tissue in the region of the optic thalamus and the ruptured vessel cannot be traced. A culture from the mesenteric embolus yields an impure growth of a short chained streptococcus. The heart is enlarged, the ventricles participating equally. The valves of the right heart are normal. The chordæ arising from the posterior papillary muscle of the mitral valve are buried almost completely in thick casings of vegetation, which join up with other vegetations on the valve margin. The valve is not stenosed. The wall of the aorta is normal and the coronary arteries arise normally.

The aortic cusps, almost equal in size, are extensively diseased (Figs. 5 and 26). The margin of the posterior cusp is, for the most part, buried in firm nodular vegetations, which extend some distance down the ventricular surface of the cusp. A large mass of vegetation of similar character involves the left anterior cusp: there is a small mass inside commissure C, and another on the free margin of the right anterior cusp. Apart from thickening of the cusp margins, commissures B and C are normal. Commissure A is curiously formed. It is triangular in plan and in transverse section, having below a breadth and depth of about a centimetre. Its depth is increased by the presence of a smooth and rounded cord of tissue, which is attached above and below, but not in its centre. The margins of the left and right anterior cusps together form a continuous curve, broken, however, by a depressed area opposite commissure A.

The upper transverse sections through this commissure show a collection of dense connective tissue infiltrated with limesalts, and overriding the aortic media. A little lower the cord becomes free; it is a fibrous strand, sheathed completely by an elastic layer and subendothelial tissues; in the main fibrous thickening of the ridge there are remnants of elastic tissue, but

few signs of active inflammation. When the region of the cusp margin is reached, the section consists mainly of dense connective tissue, interspersed with irregular strands of elastic tissue and areas of active inflammation; the infiltration is most intense under a superficial vegetation. The distortion of the issue layers is so great that the outlines of original structures are not definable.

The upper part of this commissure resembles those fused by inflammation; the free strand, with its complete elastic sheathing, probably represents one of the original cusp margins, perforated or possibly naturally fenestrated (as in Fig. 21, commissure *C*). We regard the structure as a whole to be probably the product of inflammation, though it is not possible to state quite definitely that a developmental anomaly is not also concerned.

The recognition of a congenitally malformed valve.

The specimens described in this section of our paper (*Cases 5 to 14*) were all taken from subacute or chronic infective endocarditis. They belong to a series of consecutive postmortems of this disease, numbering 31 (*Cases 5 to 35*) of Table VI. Every fused commissure in this series has been minutely examined; and we have described in detail all those which present changes of an unusual kind, and now proceed to summarise those criteria which enable us to recognise fusions which arise as congenital anomalies.

In cases where the valves are not the seat of subsequent inflammatory disease, congenitally malformed valves are usually easy to recognise, because the normal aspect of the valve, as Launois and Villaret²⁷ express it, is maintained. The type which presents two complete and undivided cusps of approximately equal size, the less common variety, is identified as congenital most readily. But where endocarditis subsequently supervenes, the nature of the deformity may not always be manifest.

The commissure affected. An analysis of past records (Table II) seems to show that commissure *A*, that which stands between the left and right anterior cusps, is undeveloped, or but partially developed, in approximately twice as many instances as is commissure *B*, and that commissure *C* is only rarely the seat of a congenital anomaly. Our own observations, summarised in Table III, agree with this conclusion; in the 11 cases which we have described in detail (*Cases 1 to 4*, and *7 to 13*), the defect occurred 7 times in commissure *A*, and 5 times in commissure *B*, never in commissure *C*. To Table III we have added our instances of conspicuous inflammatory fusion. If we include *Case 14*, there are 13 instances of fusion (*Case 18* being excluded). Of these, 6 show fusion of commissure *A*, 8 of commissure *B*, and none of commissure *C*. The relative freedom which commissure *C* enjoys, both in the congenital and inflammatory series, remains unexplained.

It is clear, from the data given, that while a preponderant affection of commissure *A* in a series of cases would speak for some, at least, of the lesions being congenital, the particular commissure affected cannot be used in any given case as a criterion of its pathology.

Subdivision of one cusp. The absence of a dividing ridge or frænum, and the absence of an angular break in the sweep of the larger cusp's line of attachment, have been used,⁴⁰ and rightly, as arguments favouring a congenital origin. With less reason, the presence of these signs has been urged as an argument in the same direction. A ridge or frænum partially subdividing one of two cusps, and an angular break in its line of attachment can be used only to argue that the valve was not laid down originally as two perfect and equal cusps. A ridge or frænum may indicate imperfect development or it may indicate inflammatory fusion.

TABLE III.
Aortic measurements.

Case.	Age.	L. A. cusp.	R. A. cusp.	P. cusp.	Total.
<i>Congenital fusion</i>					
1	10 w.	9.5	9	8.5	27
2	Adult	31	37	combined	68
3	31	20	20	38	78
4	68	51	27	29	107
<i>Congenital fusion and infective endocarditis.</i>					
7	37	32	combined	32	64
8	40	28	26	20.5	74.5
9	33	34	25	22	81
10	28	15	17.5	30.5	63
11	30	51.5	24.5	2	74
12	32	20	21	23	64
13	24	17	18	28	63
<i>Probably inflammatory fusion and infective endocarditis.</i>					
14	32	26	28	29	83
<i>Inflammatory fusion and infective endocarditis.</i>					
5	27	21	20	23.5	64.5
6	35	19	22	20	61
15	44	20	20.5	27	67.5
16	32	19.5	23	25	67.5
17	42	26	29	32	87
18	38	19.5	30	29	78.5
19	38	23.5	28	26	77.5
20	49	21	22	27	70
21	26	18	20.5	20.5	59
22	50	30	36	28	94
<i>Inflammatory fusion, healed.</i>					
37	57	27	25	24.5	74.5
38	38	25	35	25	85
39	14	16	18	18	52

All cases incorporated in this table were of male sex, with the exception of *Case 1*, in which sex is unknown. The cusps were measured along the borders of the sinuses of Valsalva, from the centre of one commissure to the next. The partial fusion of two cusps, *etc.*, separation by a ridge only or by a septum composed of fused cusp margins, is indicated by a horizontal line joining the corresponding cusp measurements.

Form of the dividing line. In congenital cases the dividing line is usually marked by a single ridge, 1 or 2 mm. in depth, 2 or 3 mm. broad, and having almost parallel borders which extend from the border of the sinus, or a little below it, either to the attachment of the cusps, well on to the cusp, or to its margin. Not infrequently this ridge divides into two, or sends off two lateral subsidiary ridges just above the attachment of the cusps (see Figs. 4 and 5), and these diverge and proceed for a variable distance on to the cusp. The main and subsidiary ridges are smooth, and of almost uniform depth, unless they have subsequently become the seat of inflammatory or degenerative processes. Ridges of this kind have always proved, in so far as they have been examined in detail, to result from congenital malformation.

Size of cusps. Dôteindre¹⁴ states that the subdivided cusp of congenital origin is larger than a normal cusp, but smaller than two normal cusps; a statement which summarises a mass of evidence and opinion. The measurements in our own cases are given in Table III. In *Cases 3, 4 and 10*, the combined cusps together measure only a little more than the remaining cusp. In *Cases 9, 11 and 13*, the difference in the sizes of the three cusps is less conspicuous, but is in the same direction; in *Cases 1, 8 and 12*, difference in sizes is inconspicuous. The unaffected cusp is always larger than either part of a combined cusp. In the remaining two cases (*Cases 2 and 7*) two undivided cusps were equal or almost equal in size. The usual size of an adult aortic cusp is about 21 to 23 mm. (see Table IV); the inequality of cusps

TABLE IV.
Aortic measurements. (Controls.)

Age.	Sex.	L. A. cusp	R. A. cusp	P. cusp	Total.	Cause of death.
48	M	23	32.5	27	82.5	Acromegaly (cor bovinum).
18	M	15.5	21	21	57.5	Pulmonary tuberculosis.
35	M	20	25.5	21	66.5	Encephalitis.
14	M	14	17	17	48	Osteomyelitis.
50	F	26	26	19.5	71.5	Diabetes mellitus.
45	F	22	25	21.5	68.5	Abdominal carcinoma.
50	F	22	21	21	64	Carcinoma of uterus.
45	M	21	23	20	64	Lobar pneumonia.
54	F	23.5	25.5	22	71	Sarcoma of uterus.
37	M	21	23.5	19	63.5	Interstitial nephritis.
41	F	24	22	20	66	Ruptured uterus.
49	M	26	25.5	22.5	74	Duodenal ulcer.
44	M	24.5	23.5	24	72	Cerebral hæmorrhage.
Averages		21.7	23.9	21.2	66.8	

which are fused congenitally is usually more correctly described as an enlargement of the unaffected cusp, rather than as a diminution in the size of the fused cusps. In inflammatory fusion inequality is not the rule; when it occurs the largest cusp is often one of the two combined cusps. It is to be observed, however, that inequalities, sometimes gross inequalities, are

found apart from fusion (see *Case 18*, Table III), and in hearts in which the valves have not been the seat of disease (the first and second cases of Table IV).

To sum up, it may be said that the rule stated by Détéindre has value, if used circumspectly.

Architecture of the cusps. To acquire a knowledge of a bicuspid valve's architecture is the most effective method of differentiating the congenital type from that formed postnatally. In the case of two undivided cusps of congenital origin, each has the complete architecture of a normal cusp. In the case of partial subdivision, the defective commissure has peculiarities which stamp it as a malformation. The union of aortic media and annulus fibrosis has been laid down abnormally: the media joins the annulus proper—meaning by annulus proper annulus quite free of elastic fibres—at an unusually low level; the union is not, as in the normal valve, immediately in the neighbourhood of the top of the commissure, but usually half way down the commissure, or even at lower levels (see Table V). Further, the upward projection of the annulus does not usually run superficial to the media, when the two layers overlap; it runs deep to it (*Cases 1, 3, 8, 12 and 13*) or less usually the junction is a straight or an almost straight one (*Cases 4 and 10*). In *Cases 9 and 11* only was the overlap in the usual direction, and in both these it was trifling in extent. The usual direction of overlap in the congenitally defective commissure, while it is the reverse of that prevailing at the normal commissure, is the same as that obtaining in the normal valve in the centre of the cusp (see Fig. 6). It thus happens that the media descends the commissure superficially to a much lower level than is the case in the normal valve; in not a few instances it descends to a much lower level than normal, both superficially and deeply.

In most normal commissures just above their beginnings, the elastic laminae of the media, though wavy, progress uninterruptedly across a transverse section, but when the upward prolongation of the annulus is about to be encountered, these laminae are thrown into curious whorls over a limited area, which forms the actual junction of media and annulus. Amongst continuous laminae are numerous fibres cut obliquely, or at right angles (Figs. 6, 7 and 12 IV). In other instances the whorling may be of a more disorderly character. At the sides of the annulus the elastic elements tend to radiate into the annulus at the junction. The disturbance of the elastic laminae, which we term whorling, is sometimes more extensive in normal commissures, especially when the commissure tends to be prolonged as a ridge above the border of the sinus of Valsalva; the elastic tissue of this ridge is then whorled. In congenitally defective commissures, a whorled media is often much more extensive and is found to constitute the chief tissue of the ridge many millimetres *below* the level of the border of the sinus. As the commissure is traced downwards the elastic elements usually begin to thin out shortly after whorling is encountered, though this is not always the case; nevertheless, the whorled character is continued. In many instances the same arrangement is seen in the annulus itself for some distance

past the line of its junction with the attenuated elastic media; so that it would seem as if the whorling is not primarily in the elastic elements but in the connective tissue supporting them. The diminution of elastic fibres is not infrequently most prominent for a while in the central layers of the congenital ridge, as this is traced down (as displayed in Fig. 12 at W), an appearance which is not seen in normal commissures; for in these the diminution occurs first in the superficial layers of the media. In commissures fused by inflammation whorling may be in evidence, but the whorled tissue occupies the position of that found in normal commissures, and is less extensive than that seen in the malformed commissure.

The subdividing ridge of the congenital commissure is essentially a projection of the tissues of the fibrous annulus, and of the main fibrous layer of the valve; so are the subsidiary ridges. The upper portions of the ridge are probably projections of the connective tissue of the media. The out-

TABLE V. *Measurements of commissures.*
Congenital series.

Case and commissure.	Ridge joins cusps attachment.	Pure annulus begins.	Medial elastic laminae end.	Overlap of annulus and media in mm..
1 B	6*	6 <i>deeply*</i>	7 <i>superficially*</i>	1 reversed
3 A	14	3 <i>deeply</i>	12 <i>superficially</i>	9 reversed
4 B	20	13	13	0
8 B	10	7.5 <i>deeply</i>	10 <i>superficially</i>	2.5 reversed
9 B	9	7.5 <i>superficially</i>	8 <i>deeply</i>	0.5
10 A	17.5	9	9	0
11 A	15	7 <i>superficially</i>	8 <i>deeply</i>	1
12 A	17	6 <i>deeply</i>	10 <i>superficially</i>	4 reversed
13 A	13	7 <i>deeply</i>	10 <i>superficially</i>	3 reversed

Inflammatory series.

Case and commissure.	Fusion ends.	Pure annulus begins superficially.	Medial elastic laminae end deeply.	Overlap of annulus and media in mm..
5 A	7*	2*	6*	4
5 B	12	2.5	6.5	4
6 A	9	1	10	9
8 C	4	0	9	9
13 B	8	0	7	7
15 A	11	3	6	3
16 B	9	2.5	10	7.5
17 A	15	3	9.5	6.5
29 A	10	3	10	7
38 B	14	2.5	10.5	8

* In these columns the distance of the point named from the upper border of the sinus is given to the nearest millimetre or half-millimetre.

growth* of the annulus, and of its covering layers, to form the commissural cusp margins appears to have undergone arrest in greater or lesser measure. The several normal layers of one cusp consequently pass uninterruptedly into those of the second, across the region where, normally, the commissural space would break them.

It is to be remarked that in the past foetal endocarditis, as an alternative cause of fusion, has frequently confused the issue^{4 13 43 44 45}; many cases have been regarded as resulting from foetal endocarditis, notably, in that described by Mönckeberg,³⁷ a case closely resembling our *Case 1*. Some writers have even gone so far as to attempt to differentiate on a purely macroscopic basis between valves malformed and those fused by prenatal endocarditis.⁴ Of recent years foetal endocarditis has been regarded less and less as the responsible cause of congenital defects,^{72 and 73} generally. There is no evidence that prenatal endocarditis produces the fusion described in this article; and in the eleven congenital cases which we have studied microscopically there has been invariable and unmistakable evidence of faulty building. If cusps are laid down in normal fashion, and subsequently fuse, whether prenatally, or postnatally, traces of the original normal architecture would be found in the region where the union has occurred; and the line of supposed union could not be comprised of layers continuing unbrokenly into each of the normal layers constituting the combined cusp.

RELATION OF INFECTIVE ENDOCARDITIS TO CONGENITALLY BICUSPID AORTIC VALVES, AND TO OTHER ANTECEDENT VALVULAR DEFECTS.

Incidence of infection in bicuspid aortic cases. The frequency of endocarditis in collected cases of bicuspid aortic valves has been commented upon by many writers. Amongst Osler's 7 cases⁴⁰, 2 manifested recent infection. Amongst Babes' 5 cases⁴, 2 and perhaps 3 were similarly affected. Two cases illustrated by Perls⁴⁹ were unquestionable cases of subacute infective endocarditis as we now recognise it, and many others of this class might be cited. Amongst de Vries' collection⁶⁷ of 13 cases, recent endocarditis was present in no less than 6. All these writers comment upon the liability of bicuspid aortic valves to subsequent inflammatory disease. That the percentage incidence of subsequent endocarditis amongst such cases is a high one is not in doubt. Of the 33 cases of congenital bicuspid valve, analysed in Table I, only three cases (5, 10 and 15) are stated to have shown endocarditis; but many of these 33 specimens were from quite young children. In the whole group of 116 cases, age is stated, or indicated, in 101. Of 32 cases under 20 years of age, 3 or 9 per cent. showed vegetations at death: of 69 adults, 16 or 23 per cent. are stated to have presented vegetations. Thus, it seems clear that 23 per cent. of all subjects possessing

*The optional view, which may be held with equal justification, namely, that the aortic wall expands away from the developing cusp margins, which are not necessarily outgrowths from it, would not affect the trend of the argument.

bicuspid aortic valves acquire infective endocarditis after reaching adult life.* This fact calls for explanation and leads us to conclusions of importance. How does the congenital malformation predispose to infection? Functional inefficiency of the heart can hardly be called to account in this instance, as it might in other forms of congenital malformation in which endocarditis is also known to supervene with more than ordinary frequency, for the lesion from the functional standpoint is trivial. It is true that signs of regurgitation sometimes manifest themselves in the uncomplicated congenital malady, but regurgitation is, in the rule, absent or slight; an inconstant or slight functional defect will not reasonably explain failure in the defences of the body: it does not explain how organisms are able to enter the blood stream and to hold their own there. The alternative conclusions appear to be either that the organisms enter the blood stream in a similar percentage of all adult subjects, or that, associated with the congenitally malformed valve, a congenital defect in the general defences of the body to the entry of organisms exists. The last view offers no attraction: it fails to explain the central fact that it is the aortic valve which becomes the seat of disease; it is negatived by the widely accepted predisposition of valves, the seat of chronic acquired disease, to similar infections. The first conclusion is the true one. The entry of organisms into the blood stream cannot be regarded as determining the disease, though it is a necessary link in the chain of events. The determining cause is the defective valve which in some way traps and holds the organisms once they have entered. From the standpoint of pathology the importance of the bicuspid valve group is that it indicates the frequency with which innocuous invasions occur amongst the general population. As infective endocarditis is responsible for death in but a very small percentage of adults generally, and as we can conclude that in these invasion of the blood stream is a common event,† we are forced to the further conclusion that such invasions are encountered in the great majority of instances without mishap. Relatively, the normally developed subject is highly immune to the disease, when he is compared with the bicuspid aortic subject, not because the organisms entering are of the wrong kind, not because they enter in insufficient numbers or possess insufficient virulence, not because appropriate general defences are called into play, but because his aortic valve presents no peculiar susceptibility to the lodgment and tenancy of organisms. The same line of reasoning minimises the importance of so-called primary foci of local suppuration in this group, as a cause of established endocarditic infection.

So much for the question of entry, with which the bicuspid condition of the valve has nothing to do. So far as lodgment is concerned, we are aware that the deformed valve forms an invariable site, almost certainly it is

* The true percentage is probably a higher one, as many cases of bicuspid aortic valve, when associated with subacute infective endocarditis, are, to our knowledge, overlooked. It is also to be noted that we include no cases in the collection of 116 which are described under the heading of endocarditis.

† Meaning that it occurs in many adults.

always the initial site of valve lodgment. The rôle played by the bicuspid valve is that it provides a suitable trap for organisms which apparently enter the blood stream not infrequently.

These are the conclusions at which we arrive when we consider the incidence of infective endocarditis in the group presenting a bicuspid aortic valve: but when the relation is viewed from this standpoint alone, and the accepted rarity of the congenital defect is borne in mind, the full significance of the association is not displayed.

Incidence of the bicuspid valve in subacute infective endocarditis. If we approach the problem from the opposite angle and, confining ourselves to subacute infective endocarditis, ask how often bicuspid valves of congenital origin are encountered in this disease, an equally, if not more, important relation is established. The specimens which have been described were taken from 31 consecutive postmortems upon patients dying of this form of endocarditis, and these are summarised in Table VI. Amongst the 31 cases certainly 8 (or 26 per cent.), and perhaps 9 (*Case 14*), presented congenitally bicuspid valves. If we exclude from the total those cases in which the aortic valves were only slightly affected, or escaped infection, then we have to deal with 20 cases, and the incidence of bicuspid valves is 40 per cent. This remarkable figure may actually prove to be higher or lower than that which truly represents the relation; but that it does not depart widely from the true value we feel assured from our past experience of subacute infective endocarditis; for we were impressed by the frequent incidence of fusion which we now recognise to be the commonest congenital type in autopsies antedating this particular collection. Our observations are also supported by those of Beneke⁷⁹, who states that in cases of subacute infective endocarditis observed during the war quite a high percentage showed fusion of the right and left anterior cusps of the aortic valves; he argues from the last fact that the fusion was congenital, and that it had predisposed the subject to infection*. Further, we have inspected several collections of subacute endocarditis specimens, and find the bicuspid valve to be frequent amongst them. Thus of 16 specimens in the museum of the Royal College of Surgeons, London, which, judged from the lesions they present, appear to be undoubted cases of subacute infective endocarditis, no less than 7 certainly, and perhaps 8, show fusion of two cusps similar to those ascertained to be congenital. Of these, 1 specimen presents complete fusion and 6 present partial fusion. In the same collection a seventeenth case, which is probably from a subacute infective, also shows a bicuspid aortic valve. Of the 17 cases, 11 cases show heaviest involvement of the aortic valve or equal involvement of aortic and mitral valves; the 8 instances of congenitally fused cusps occur exclusively in the last group. This collection is of particular value in that the specimens were nearly all placed in the

* Kaboth's dissertation, in which Beneke states these observations were recorded at length, is not available to us.

TABLE VI.

Summary of lesions in 34 cases of subacute infective endocarditis in male subjects.

	Involvement of					Commissure fused*	Remarks.
	Aortic valve.	Septum.	Mitral valve.	Chordae.	Post. wall left aur.		
5	H	sl.	sl.	no	no	—	Rheumatic
6	H	v.sl.	H	yes	no	—	
7	H	no	sl.	no	no	A absent	
8	H	sl.	v.sl.	no	no	B	
9	H	no	sl.	yes	no	B	
10	H	no	sl.	..	no	A	
11	H	no	H	..	no	A	
12	H	sl.	H	..	no	A	
13	H	v.sl.	H	..	no	A	
14	H	no	H	..	no	A?	
15	H	sl.	H	..	yes	—	{ Syphilitic aortitis
16	H	no	H	..	no	—	
17	H	no	H	..	no	—	
18	H	sl.	H	..	yes	—	
19	H	sl.	H	..	yes	—	
20	H	sl.	sl.	..	no	—	
21	H	H	H	..	yes	—	
22	H	sl.	H	..	no	—	
23†	H	no	H	..	no	A	
24	H	H	H	..	no	—	
25	sl.	sl.	H	..	no	—	Rheumatic
26	sl.	no	H	..	no	—	
27	no	no	H	..	no	—	
28	v.sl.	no	H	..	yes	—	
29	sl.	sl.	H	..	no	—	
30	v.sl.	no	H	..	yes	—	
31	no	no	H	..	no	—	
32	no	sl.	H	..	yes	—	
33	no	sl.	H	..	yes	—	
34	no	no	H	..	no	—	
35	no	no	H	..	yes	—	

H = heavily affected; sl. = slightly; v.sl. = very slightly.

museum many years ago; they were not placed there because of the bicuspid state of the aortic valve which does not figure in the catalogue notes; they stand in the section of endocarditis exclusively. Dr. Hubert M. Turnbull has very kindly shown us 7 unselected hearts from patients dying of subacute infective endocarditis recently at the London Hospital. In all these cases the aortic valve was heavily involved by the disease; and in 3 of the specimens a bicuspid condition of the valve, of congenital form, existed. Dr. Turnbull tells us that the frequent association between infective endocarditis and fused aortic cusps has been remarked upon by Dr. W. W. Woods in his laboratory.

* In this column the letter A or B indicates the commissure fused congenitally.

† The heart of this patient has not been examined histologically because, prior to our beginning these studies, it had been set up as a museum specimen. The fused commissure is almost identical in appearance with that of Case 10.

If these figures can be regarded as at all representative, the first conclusions to be derived from these observations are that in cases of subacute infective endocarditis, in which the aortic valve is more than slightly affected (a group presumably including all those in which this valve is primarily involved), a congenital defect of the valve, almost as often as not, is the determining cause of the disease; and that in the disease treated without qualification a congenital malformation of one valve is responsible for the final disease in a quarter of the cases, if not in a greater proportion. The last figure we give with some reserve, in that heavy involvement of the aortic valve may, perhaps, be over-represented in our series. Thus Libman's⁷¹ proportion for involvement of the aortic valve is less than our own.

Antecedent defects of the valve as a determining cause of subacute infective endocarditis. We have arrived at the conclusion that, in a very appreciable number of subacute infective endocarditis cases, neither the strength nor the quantity of the poison introduced into the system, nor weakness in the general defences of the body, determine the disease. The disease is determined by an antecedent, local, valvular defect. This conclusion approaches, if it does not reach, finality for the group considered; the lesion with which we are dealing is manifestly congenital: the conclusion, therefore, founds itself upon a demonstration, not upon an opinion.

Now, so far as infective endocarditis is concerned, the subacute variety of the disease may be regarded as of a distinctive kind. It is peculiar in that, while running a fatal course, this course is remarkably protracted.* The virus having gained a foothold is for long periods lethargic; the symptomatic reactions of the patient to this virus are inconspicuous in all but the terminal stages of the disease; the tissues react locally, and manifest abundant signs of partial healing, though healing in the complete sense, such healing as would extirpate the disease, is scarcely known to occur. This history of the disease in the individual case is the history of a long drawn struggle, in which fluctuating improvements in the well being of the patient often appear, and in which often enough the end actually comes through such an accident as embolism, or through an intercurrent infection, or through renal deficiency. This picture contrasts with the remaining forms of infective endocarditis; in these, the symptoms of poisoning dominate; the course is short, local evidences of healing are almost absent, and the patient sinks steadily and rapidly.

Consider the pathology of the first type of malady as a general proposition; we know little enough of it, it is true; but it has been shown that in an appreciable number of the cases the pathology is peculiar in that the disease is determined by a local defect. That is almost certainly not the

* In this respect it is to be observed that the histories of the cases now published are deficient and, therefore, unrepresentative. A minimal, but not a maximal, period for the course has been determined in each case.

case for the second or acute type. We can find no evidence, though we have searched, of any particular predisposition of bicuspid aortic cases to acute endocarditis* ; and, as is well known, the last lesion is often, if not usually, but a part of a more widely distributed disease, a pneumococcal or staphylococcal process for example, of which the original site of the entry is evident. By common consent the subacute disease is in an overwhelming majority of cases streptococcal, and the primary site of the body's invasion is obscure. Again, while acute endocarditis not infrequently affects the valves of the right heart, the subacute disease almost confines itself to the chambers of greater strain†.

Since it appears to be the case that, in the bicuspid aortic group, a peculiar pathogeny is associated with a peculiarly insidious course, the more general conclusions, that peculiar pathogeny and peculiar course are directly related, and that all cases of the subacute disease are determined in a similar fashion, cannot avoid very full consideration. The final demonstration that a congenital malformation determines the disease in a by no means negligible proportion of subacute infective endocarditis cases, in view of these possibilities, throws antecedent defects in the valves temporarily into the foreground of the more general discussion. In speaking of a relation between the pathogeny and course, we have in mind such a possibility as the following. The organisms are organisms to which the body is already accustomed before they attack the valve ; relative to the general defences of the body they are not of a high grade of virulence ; in the fight for dominance there is almost a balance between the virus and the defence, and it is only because the valve offers to the organisms a suitable redoubt that they are able to entrench and to establish themselves. If this conception truly represents the beginning of the disease, then the subsequent peculiar course would become more intelligible.

A succeeding investigation should further explore those cases of subacute infective endocarditis, in which a bicuspid aortic valve is not found ; a group which still holds, perhaps, three quarters of the cases. For example, it is conceivable that minor congenital defects, more easily overlooked than those with which we have been dealing, may contribute their quota, and such defects would not necessarily lie in the aortic valve. We are inclined, however, to reject the last as improbable. The congenital defect in the aortic valve is essentially in the commissure, as has been shown ; yet it is not the commissure which is attacked by the disease ; it is the rule that the lines of apposition of the cusps, and later the bodies of the cusps, are the chief seats of disease. It is difficult, therefore, to link up the point of attack with the point at which the congenital defect is concentrated. It seems more

* In so far as the group of 116 collected cases are concerned the case reports rarely allow us to distinguish the variety of endocarditis when this was found. We rely for our present statements upon our own observations.

† We are not personally conversant with subacute disease occurring in the right heart, apart from defects in the septum between the right and left chambers, though it is possible that it happens on occasion.

probable that the defect predisposes, not in virtue of the manner in which it originates, but in virtue of secondary changes which it brings in its train. By the time adult life is reached, most, if not all, of these malformed valves are thickened at their margins or more generally, perhaps they are more vascular than normal valves.

If these secondary changes in reality predispose the valve to infection, such a fact would form a connecting link between the susceptibility of the malformed valve on the one hand, and that of the valve which is the seat of antecedent *acquired* disease on the other.

That antecedent acquired disease predisposes to subacute infective endocarditis is well recognised, but we are yet far from knowing accurately the numerical relation. Of those cases in our series of 31, in which a congenitally bicuspid aortic valve was not found, 2 presented syphilitic aortitis (Cases 25 and 26, Table VI): in other instances the histories and lesions were compatible with healed rheumatic endocarditis. In the remainder, old thickening of the valves, at points unaffected by vegetations, was invariable. There would be no difficulty in preparing a case, based largely upon *opinion*, which would represent a large number, if not all, of these valves, as being previously diseased. When, however, we come to study in detail the morbid anatomy and histology in the non-congenital cases of our series, we find ourselves too often unable to state with *certainty* the extent to which the changes represent damage antecedent to the subacute infection, and to what extent they represent local healing, or secondary thickening, during the course of the final malady itself, a point to which attention has been drawn earlier in our paper: an expression of opinion on such matters does not suffice.

While the conclusions drawn in respect of the bicuspid aortic valve group appear to us to be drawn with finality, similar conclusions in respect of antecedent acquired disease cannot be drawn with finality in the present stage of knowledge. Nevertheless, we feel ourselves attracted towards the more sweeping conclusions, and make this confession in the hope of stimulating further and exact observations directed towards the proof or disproof of the suggestions put forward.

SUMMARY AND CONCLUSIONS.

1. The normal structure of the aortic valve, and especially the relation of the aortic media to the annulus fibrosus, is described.
2. Four cases of congenitally bicuspid aortic valves, and seven further cases associated with subacute infective endocarditis, are described in detail and past records of bicuspid aortic valves are analysed.
3. The criteria differentiating congenital from inflammatory fusion are discussed, and defined.
4. Bicuspid aortic valves, formed antenatally, are malformations; it is not known that they can result from foetal endocarditis.

5. Amongst males reaching adult life, and possessing congenitally bicuspid aortic valves, 23 per cent. at least die of active endocarditis.

6. In an unselected series of 31 cases of subacute infective endocarditis, 26 per cent. presented a congenitally bicuspid condition of the aortic valves: amongst these of the 31 cases in which the aortic valve was more than slightly involved by vegetations, 40 per cent. presented the bicuspid malformation.

7. If these figures, and others used in support of them, may be taken as representative, or nearly representative, it follows that a congenitally bicuspid aortic valve often determines subsequent subacute infective endocarditis, and especially so in cases in which the aortic valves are first involved by this disease.

8. We conclude that in a by no means negligible proportion of cases of subacute infective endocarditis the facility which the organisms concerned enter the blood stream, their numbers and their virulence, are not factors of prime consequence. In this same group, neither the presence of local foci of infection nor weakness in the body's immunising defences, before the organisms invade the blood stream and obtain a foothold in the valves, can be regarded as important contributory causes of the disease. The determining cause is a susceptibility of the valve: the invasion by organisms is almost physiological. We suspect, though we are not yet able to prove, that these same conclusions may apply to all cases of subacute infective endocarditis.

We are indebted to Dr. G. W. Goodhart for all blood examinations included in this report.

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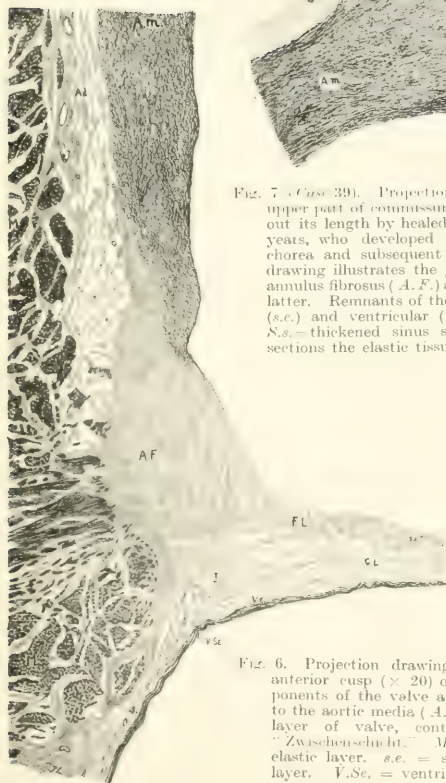


FIG. 6. Projection drawing of a section through the centre of the right anterior cusp ($\times 20$) of a normal heart: to show the chief components of the valve and the relation of the annulus fibrosus (A.F.) to the aortic media (A.m.). *Ad.* = aortic adventitia. *C.L.* = central layer of valve, continued from *I.*, the intermediate layer or "Zwischenschicht." *M.* = ventricular muscle. *E.* = elastic layer. *s.e.* = sinus elastic layer. *V.e.* = ventricular elastic layer. *V.Se.* = ventricular subendothelial layer.



FIG. 7 (Case 39). Projection drawing of a transverse section through the upper part of commissure *B1-20*, tised into a low triangle throughout its length by healed rheumatic endocarditis. From a boy of 14 years, who developed aortic regurgitation following an attack of chorea and subsequent rheumatic fever 2 years before death. The drawing illustrates the junction of the aortic media (A.m.) with the annulus fibrosus (A.F.) and shows the normal upward projection of the latter. Remnants of the fibrous layers (F.L.) and of the sinus elastic (s.e.) and ventricular (V.e.) layers of the cusps are plainly visible. *S.s.* = thickened sinus subendothelial layer. In this and succeeding sections the elastic tissue is most deeply stained.



FIG. 8 (*Case 1*). Peacock's case. A retouched photograph, twice natural size. Commissures A and B are fused, C is normal. L.A. and R.A. and P. = left and right anterior and posterior cusps respectively. R.C. = mouth of right coronary artery. *i* = incisure at end of commissure B. *lf* and *rf* = folds binding the end of commissure A, *r* and *f* = main ridge and subsidiary fold of commissure B. *In.* = innominate, *Ca.* = carotid and *S.* = subclavian artery. The retouching of this and succeeding photographs has been done with close attention to the original specimen and only to remove photographic defects.

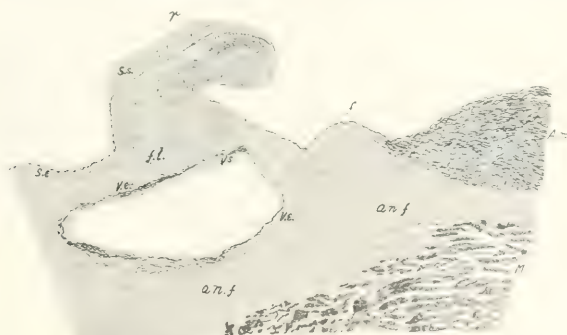


FIG. 9 (*Case 1*). Projection drawing of a transverse section of commissure B along the line shown in Fig. 8 ($\times 40$). A.m. = aortic media. An.f. = annulus fibrosus. f. = small fold shown in Fig. 8 f. f.l. = fibrous layer of valve. M = muscle of ventricle. s.e. = sinus elastic layer. S.s. = sinus subendothelial layer. V.e. = ventricular elastic layer. V.s. = ventricular subendothelial layer. r = main ridge (see Fig. 8 r).



Fig. 10 (Case 38). Projection drawing of a transverse section through a fused aortic commissure (commissure *B* (15)). The patient, a man of 38 years, died of appendix abscess. The heart was not enlarged and the lesion in the aortic valve was evidently inflammatory and of old standing, producing no symptoms during life. The commissure was fused throughout its whole length, the corresponding cusps being separated by a single deep frantum. The section chosen as an illustration is low enough to pass through the upward projection of the ventricle into the commissure. The ventricular elastic layer (*v.e.*) lining this cavity on three sides is continued into the fused cusps and does not surround the cavity (as in Fig. 9). Remnants of the fibrous layers of the two cusps (*F.L.*) are distinct, and these are sheathed by the sinus (*s.e.*) and ventricular elastic (*v.e.*) layers. The cusps are cemented by firm connective tissue formed in the welded ventricular subendothelial layers (*V.Sc.*). At the base new and irregular elastic fibres (*e*) have developed.

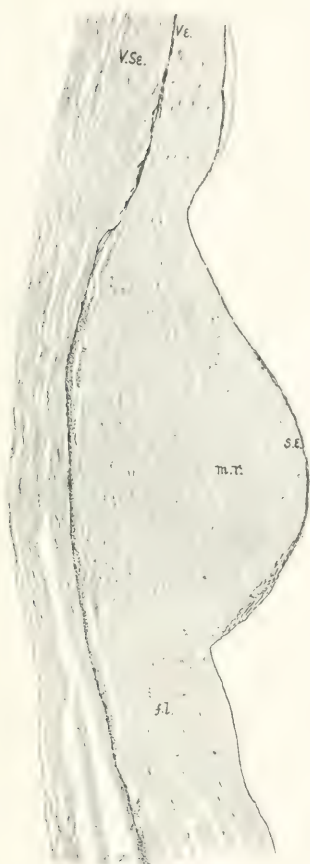


FIG. 11

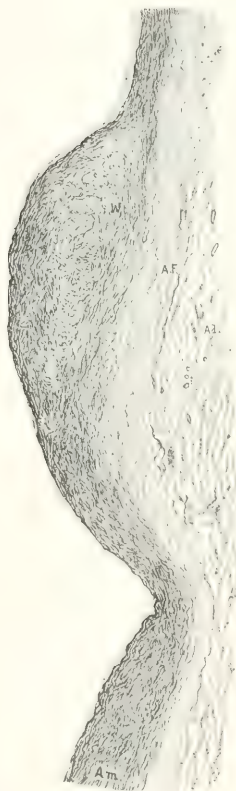


FIG. 12

Fig. 11 (*Case 3*). Projection drawing of a transverse section ($\times 100$), not far from the margin of the combined cusp, and including the continuation of the main ridge (α) of Fig. 10. *m.r.* = main ridge, *f.l.* = fibrous layer of combined cusp, *s.e.* = sinus elastic layer, *V.e.* = ventricular elastic layer, and *V.Se.* = thickened ventricular subendothelial layer.

Fig. 12 (*Case 8*). Projection drawing of a transverse section of commissure *B*, about 7.5 mm. below the border of the sinus ($\times 25$). *A.m.* = aortic media, which is whorled (*W*) and swollen to form the main ridge of the commissure. *A.F.*, the top of the annulus fibrosus, is appearing deep to the media. *Ad.* = aortic adventitial layer.



Fig. 13. (*Case 6*). Projection drawing of a vertical section ($\times 17$) through the centre of commissure A, Fig. 18. *Ad.* = adventitia of aorta. *A.F.* = annulus fibrosus. *A.m.* = end of aortic media. *B.V.* = tissue forming the base of the vegetations. *C* = end of fused commissure. *e* = new elastic fibres. *f.b.c.* = fresh blood clot. *M* = ventricular muscle. *V* = fresh vegetations. *V.e.* = ventricular elastic layer. *V.se.* = ventricular subendothelial layer, recently thickened.



Fig. 14 (*Case 2*). A photograph of the aortic valve ($\times 9.10$), showing a congenitally bicuspid condition. In this and succeeding figures the corresponding commissures are marked *A*, *B* and *C*; the right and left coronary vessels *R.C.* and *L.C.*, respectively, and the left and right anterior and posterior cusps, *L.A.*, *R.A.*, and *P.*, respectively.

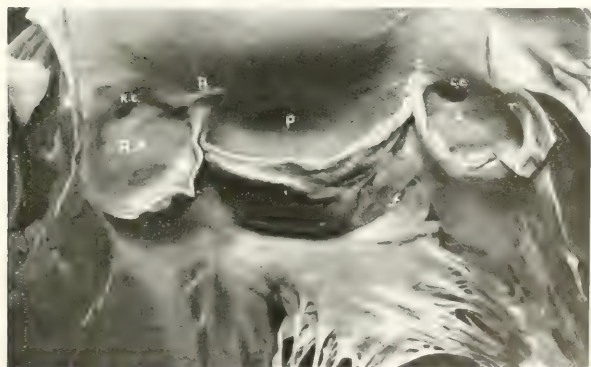


Fig. 15 (*Case 3*). A natural sized photograph of a congenitally bicuspid commissure. The combined commissure has been cut in opening the aorta; it was partly subdivided by the ridge *r*. *f* is a subendothelial thickening of the posterior cusp and base of the mitral valve.

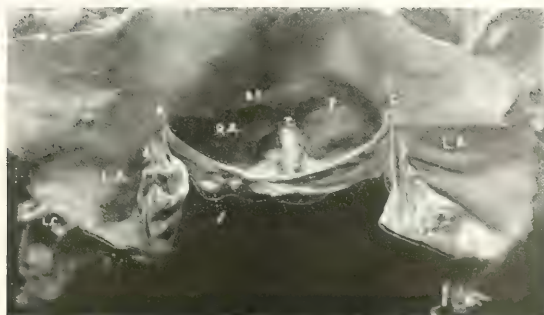


Fig. 16 (*Case 4*). A natural-sized photograph of a congenitally bicuspid aortic valve. The R.A. and L.A. cusps are combined, the imperfect commissure being represented by the ridge *c*. This ridge and the lines of attachment of the L.A. cusp are indicated by *d* and *e*. The end of another calcareous deposit is seen at *f*.

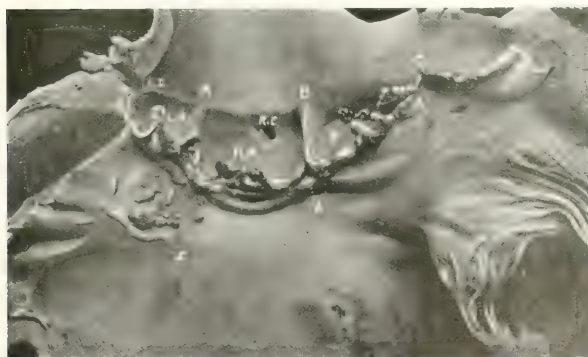


Fig. 17 (*Case 5*). A photograph of the aortic valve ($\times 5/6$) in a case of subacute infective endocarditis. Commissures A and B are fused. *b* = a small bridge of new connective tissue joining the adjacent cusps. V = vegetations on the septum. *e* is a fold of thickened endocardium.

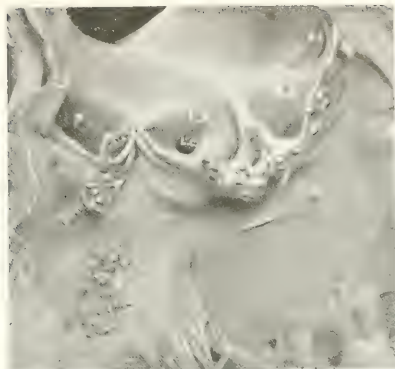


Fig. 18 (*Case 6*). A photograph of the aortic valve, a little more than natural size, in a case of subacute streptococcal endocarditis. Showing a fused commissure, *A* and a complete shell of firm vegetations beneath it. *V* = Vegetations on mitral valve.

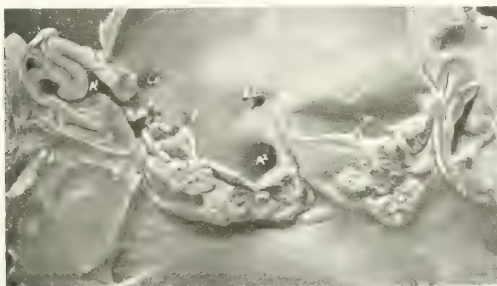


Fig. 19 (*Case 7*). A photograph slightly less than natural size, showing a congenitally bicuspid aortic valve and subacute infective endocarditis. *A*¹ and *A*² are aneurisms of the sinus. *f* = small fissure in the sinus wall.

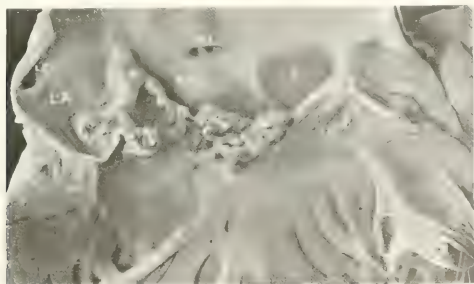


Fig. 20 (*Case 8*). A congenitally bicuspid aortic valve, shown in the photograph at a little less than natural size. The valve is the seat of old standing calcareous vegetations.

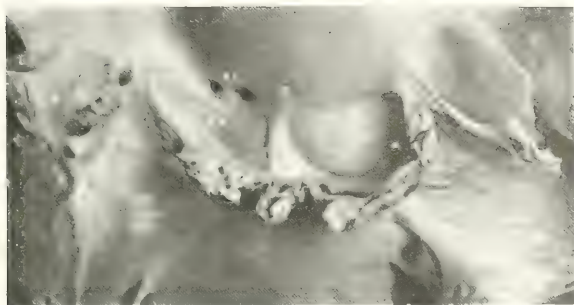


Fig. 21 (*Case 9*). A congenitally bicuspid aortic valve, shown a little more than natural size. The margins of the valve are the seat of numerous firm vegetations. *a* = aneurysm of sinus.

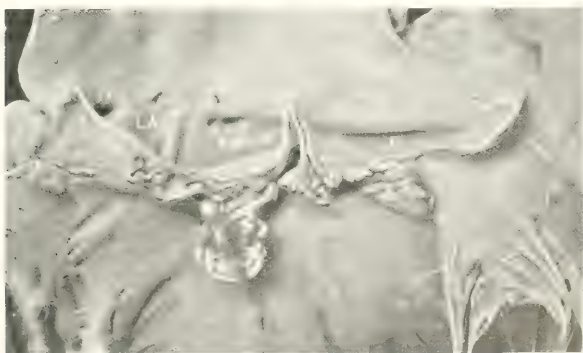


Fig. 22 (*Case 10*). A natural-sized photograph of a congenitally bicuspid aortic valve, affected by subacute infective endocarditis. *f, f* = fissures in the aortic wall.

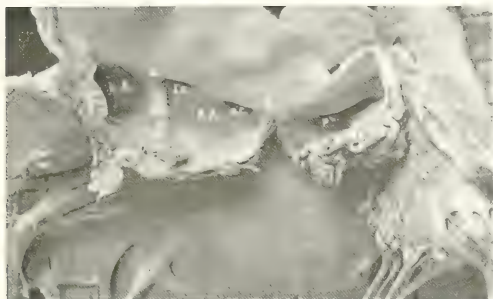


Fig. 23 (*Case 11*). A photograph ($\times 4.5$) of a congenitally bicuspid aortic valve. The defective commissure *A* is calcified, the valve margins are the seat of subacute infective endocarditis.

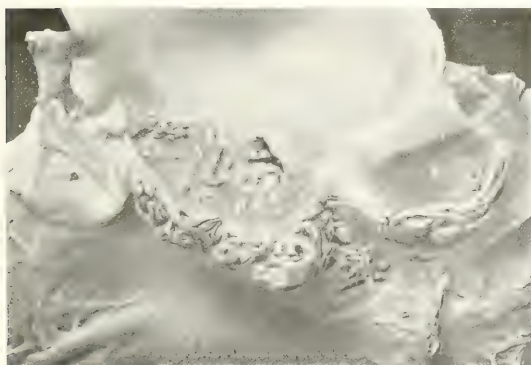


Fig. 24 (*Case 12*). A natural-sized photograph of a congenitally bicuspid aortic valve affected by subacute infective endocarditis. The sinuses are eroded by recent disease.

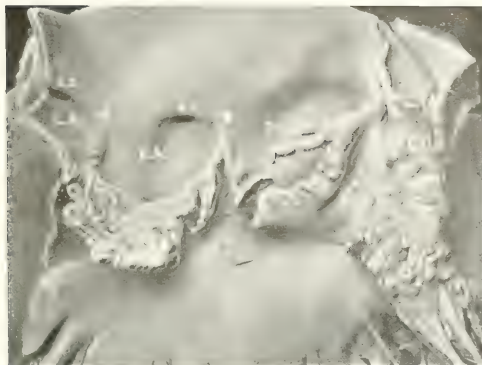


Fig. 25 (*Case 13*). A natural-size photograph of a congenitally bicuspid aortic valve. It is the seat of numerous firm and calcified vegetations.



Fig. 26 (*Case 14*). Photograph of the aortic valve in a case of subacute infective endocarditis, a little less than natural size. Commissure *A* is fused, probably as a result of inflammatory disease.

THE CAUSATION OF EXTRASYSTOLIC IRREGULARITIES OF THE HEART BEAT, WITH SPECIAL REFERENCE TO THE HYPOTHESIS OF PARASYSTOLE.*

By C. C. ILIESCU (Bucarest) and A. SEBASTIANI (Rome).

(*From University College Hospital Medical School, London.*)

IN a series of recent papers Kaufmann and Rothberger have undertaken a detailed analysis of certain extrasystolic irregularities, and, upon the basis of this analysis, have come to a conclusion which, if true, would be fundamental so far as our conceptions of these extrasystolic irregularities of the heart are concerned.

This view is not an entirely new conception, having been put forward, though in slightly different form, by Fleming.¹ It is that the isolated extrasystole is a response to one impulse of a more or less rhythmic series. The hypothesis of Fleming and of Kaufmann and Rothberger differ, however, the former regarding the extrasystolic rhythm as slower than that of the natural heart beat and analogous to or identical with the so-called idio-ventricular rhythm of complete heart block, the latter regarding it as faster than the natural heart beat and analogous to or identical with the rhythm of paroxysmal tachycardia. It is with the last conception and with this alone that we shall deal.

Before proceeding to describe this hypothesis of Kaufmann and Rothberger more fully, it must be emphasised that these writers have not as yet applied it as an explanation to all cases of extrasystolic irregularity, but to only a minority of such cases. Thus, there is a common form of extrasystolic irregularity, in which premature beats arising in the *ventricle* are accurately coupled with the regular beats at equal intervals in the curve, as for example in perfect instances of so-called bigeminy or trigeminy. It is clear that to such instances the hypothesis of Kaufmann and Rothberger is inapplicable; for the rhythm underlying the extrasystoles in such instances, would necessarily have an exact and simple mathematical relation to the rhythm providing the normal beats. This exact and simple relation,

* Observations undertaken on behalf of the Medical Research Council.

if maintained for an appreciable time, could not be explained as a coincidence; the interdependence of the two rhythms, normal and extrasystolic, or their dependence upon some common casual agencies, would have to be assumed. Briefly, if two series of rhythmic impulses are developed in the heart, and these series are entirely independent of each other and fail to interfere with each other, the chances against their presenting a simple and precise mathematical relation to each other for an indefinite period are infinite. In the case of ventricular extrasystoles the provisor of non-interference of one rhythm with the other is largely superfluous, since non-interference is actually the rule, but in the case of auricular extrasystoles this is not the case.* It is the rule that the auricular extrasystole disturbs the normal rhythm of the heart at its source.

The first² of the serial papers of Kaufmann and Rothberger contains a somewhat remarkable demonstration. They show that if in a normally and regularly beating heart, rhythmic shocks of somewhat slower* rate are allowed to fall on the auricle, the auricle will contract prematurely in response to these shocks, from time to time; they show, further, that after the first response of this kind, the remaining responses to occasional shocks will occur at perfectly regular intervals, and that an accurately repeated irregularity or "allorhythmia," as it is called, will result. The production of an allorhythmia is independent of the rate of the rhythmic shocks introduced into the auricle. Thus, it would appear that if two completely independent series of rhythmic impulses (the one normal and the other abnormal) fell upon the *auricle*, and both were capable of yielding responses at suitable intervals, a simple allorhythmia such as a bigeminal or trigeminal action would inevitably result and might be maintained indefinitely. The maintenance of such a simple allorhythmia would be due to the regular disturbance of the normal rhythm by beats belonging to the abnormal rhythm, as explained in the paper cited. Conversely, therefore, the presence of such a permanent and natural bigeminy or trigeminy of the auricle, does not preclude, as it does in the case of the ventricle, the production of this allorhythmia through the agency of two independent series of rhythmic impulses. But it must also be clear that these very simple and persistent forms of auricular irregularity cannot be used as evidence for the theory of independent rhythms; thus, if we are dealing with a simple auricular bigeminy or trigeminy, accurately repeated for long periods, it is evident that the intervals between one extrasystole and the next extrasystole to follow it (an interval which will be termed the inter-extrasystolic interval in the rest of this article), will be constant; consequently all the inter-extrasystolic intervals of the curve will necessarily present a simple mathematical relation to each other, and this relation could not be regarded as adequate evidence that these extrasystoles result from abnormal but

* Shocks of slower rate must perforce be used, otherwise the heart will respond to these shocks only.

rhythmic impulses. Instances where the intervals at which the extrasystoles occur in the curve are changeable, are alone admissible as evidence. It is examples of the last kind which are brought forward by Kaufmann and Rothberger, and it is upon the evidence of a simple mathematical relation between the interextrasystolic intervals of such curves that these writers solely rely for evidence of their hypothesis. They term extrasystolic irregularities supposedly arising as a result of occasional responses to rhythmic impulses, a *parasystolic* irregularity.

To illustrate, we give the following example of our own. Fig. 1 is a short strip of curve taken from a patient who has been under observation for a long while, and constantly presents short groups of auricular extrasystoles. In this particular curve each normal beat is followed by a pair of extrasystoles. The distance between the two extrasystoles of a pair (short inter-extrasystolic intervals) is almost always 19 fiftieths of a second; the distance between the last extrasystole of a pair and the first extrasystole of the succeeding pair (long inter-extrasystolic interval) is 56, 57, 58, or 59 fiftieths, or an average of 57 fiftieths. As there is a simple and exact relation between the short and long inter extrasystolic intervals ($19 \times 3 = 57$), this relation may be used as evidence that all belong to the same rhythmic series and are produced by an independent rhythm arising in the auricle. This example is precisely comparable to several used by Kaufmann and Rothberger. The strip of curve published is a sample of a much longer curve, the measurements of which are given in Table I. In this table the measurements are given in three columns. In the first column is the number of the beat, the extrasystoles being italicised. In the second column is the interauricular interval, these intervals which are terminated by extrasystoles being italicised. In the third column the long inter-extrasystolic intervals are shown and these are uniformly simple multiples of the shorter inter-extrasystolic interval (which in this example averages 19 fiftieths of a second); the deviation from a perfect fit is added as a + or - quantity in the third column. The table contains a larger number of measured and successive beats than any given by Kaufmann and Rothberger, and is as perfect an example as the best which they produce as evidence for their theory of a parasystolic phenomenon. Actually, the present example shows smaller deviations from a simple mathematical relation than do the majority of the curves illustrating Kaufmann and Rothberger's articles.

Their hypothesis assumes from the outset that if two rhythmic centres are active in one and the same auricle, the faster of these rhythms will not necessarily dominate, the slower will not necessarily be submerged, as is usually admitted to be the case: but that both will continue to give responses at intervals. The assumption involves the idea that the auricle does not always respond to the faster rhythmic impulses, that the centre of slower rhythmic activity is in some way guarded from the receipt of those excitation waves which are let loose by the centre of faster activity; it also

TABLE I.

All time intervals in these tables are

Number	Intervals between successive beats.	Intervals between extrasystoles.	Number	Intervals between successive beats.	Intervals between extrasystoles.	Number	Intervals between successive beats.	Intervals between extrasystoles.	Number	Intervals between successive beats.	Intervals between extrasystoles.
1	19		27	39	58	53	19		78	39	58
2	19		28	19	19×3	54	38		79	19	19×3
3	38		29	19	(+1)	55	19	19×3	80	19	
4	19	19×3	30	38		56	18		81	38	
5	19		31	19	19×3	57	38		82	19	19×3
6	38		32	19		58	19	19×3	83	19	
7	19	19×3	33	39	58	59	19		84	39	58
8	19		34	19	19×3	60	39	19×3	85	19	19×3
9	38		35	19	(+1)	61	19	(+1)	86	18	
10	19	19×3	36	38		62	18		87	38	
11	18		37	19	19×3	63	39	19×3	88	19	19×3
12	38		38	18		64	19	(+1)	89	18	
13	19	19×3	39	39	58	65	18		90	38	
14	18		40	19	19×3	66	39	19×3	91	19	19×3
15	39		41	19	(+1)	67	19	(+1)	92	18	
16	19	19×3	42	39	58	68	18		93	20	
17	19	(+1)	43	19	19×3	69	39	19×3	94	40	58
18	38		44	19	(+1)	70	19	(+1)	95	18	19×3
19	19	19×3	45	38		71	18		96	19	(+1)
20	19		46	19	19×3	72	38		97	38	
21	39		47	18		73	19	19×3	98	19	19×3
22	19	19×3	48	40	59	74	19		99	18	
23	18	(+1)	49	19	19×3	75	39	19×3	100	38	
24	39		50	19	(+2)	76	19	(+1)	101	19	19×3
25	19	19×3	51	39	58	77	19		102	19	
26	18	(+1)	52	19	19×3						

* This figure 19 is an approximate average of all the short inter-extrasystolic intervals of the table.

(Case 1.)

expressed in fiftieths of a second.

Number	Intervals between successive beats.	Intervals between extrasystoles.	Number	Intervals between successive beats.	Intervals between extrasystoles.	Number	Intervals between successive beats.	Intervals between extrasystoles.	Number	Intervals between successive beats.	Intervals between extrasystoles.
103	38		129	19		154	38		180	18	
104	19	19 \times 3	130	38	56	155	19	19 \times 3	181	10	59
105	19		131	18	19 \times 3 (-1)	156	18		182	19	19 \times 3 (+2)
106	38		132	19		157	39	58	183	18	
107	19	19 \times 3	133	39	58	158	19	19 \times 3 (+1)	184	39	
108	19		134	19	19 \times 3 (+1)	159	19		185	18	19 \times 3
109	38		135	18		160	38		186	19	
110	18	19 \times 3 (-1)	136	38	57	161	19	19 \times 3	187	39	57
111	19		137	19	19 \times 3	162	18		188	18	19 \times 3
112	38		138	18		163	39	58	189	19	
113	19	19 \times 3	139	38	57	164	19	19 \times 3 (+1)	190	39	58
114	19		140	19	19 \times 3	165	18		191	19	19 \times 3 (-1)
115	38		141	19		166	38		192	18	
116	19	19 \times 3	142	38	58	167	19	19 \times 3	193	40	59
117	18		143	20	19 \times 3 (+1)	168	19		194	19	19 \times 3 (+2)
118	38		144	18		169	38		195	18	
119	19	19 \times 3	145	38	57	170	19	19 \times 3	196	40	59
120	19		146	19	19 \times 3	171	19		197	19	19 \times 3 (+2)
121	39	58	147	19		172	38	57	198	19	
122	19	19 \times 3 (+1)	148	38	57	173	19	19 \times 3	199	40	59
123	18		149	19	19 \times 3	174	18		200	19	19 \times 3 (+2)
124	38		150	19		175	39	58	201	19	
125	19	19 \times 3	151	38	58	176	19	19 \times 3 (+1)	202	39	58
126	19		152	20	19 \times 3 (+1)	177	19		203	19	19 \times 3 (+1)
127	38		153	19		178	39	58	204	18	
128	19	19 \times 3				179	19	19 \times 3 (+1)	205		

involves the idea that when in these circumstances the auricle responds to the slower rhythmic centre, the excitation wave so arising does not disturb the rhythm of the more active centre. The last idea acquires greater significance, since in some of Kaufmann and Rothberger's examples the faster rhythm arises in the A-V node, yet it is supposedly continued in uninterrupted fashion, although this same node occasionally transmits an auricular response of sinus origin to the ventricle. The partial protection which each rhythmic centre has to enjoy from the activity of its rival, under the hypothesis of parasystole, is clearly recognised by its originators who ascribe it to local block (using the term "*Austrittsblockierung*" for the protection of the sinus rhythm and the terms "*Eintrittsblockierung*" and "*Schutzblockierung*" for the protection of the faster centre from sinus waves). We emphasise these assumptions, which so far as we can see are primarily pure assumptions, because if there were independent reasons for believing that two rhythms of widely different rate could continue to be active in one and the same heart chamber, the strength of the evidence needed to render the present hypothesis acceptable would be reduced. But there are many reasons for believing that such rhythms cannot remain active side by side, in the sense expected of them.* The conception of parasystole conflicts with generally accepted views; this does not demand its rejection, but it does demand that the evidence which is put forward to support it should be of a convincing kind and that it should include some independent testimony that the protective blocks which are assumed, actually exist. The last is not attempted: we are left with the evidence of separate and active rhythms only.

To continue an analysis of the irregularity presented by our first patient: in the first table used (Table I) the extrasystoles occur almost exclusively in pairs: at one point, however (beats 92-94), a group of three extrasystoles is found: nevertheless, the simple relation between short and long interextrasystolic intervals remains undisturbed. This curve was taken from our patient 10 minutes after the subcutaneous administration of 1.50 of a grain of atropine sulphate. A second curve from the same patient, taken under simple conditions of rest three weeks earlier, is tabulated in Table IV. It constitutes a more searching test of the simple ratio between interextrasystolic intervals, because in addition to the group of 2 extrasystoles, groups of 3 or 4 extrasystoles are not infrequent: the simple ratio is again found to exist, such deviations as occur being of a small order.

Yet this example as it stands has little value as evidence; we require evidence that under whatever conditions our patient is examined, always providing that extrasystoles remain, a simple ratio is maintained. We have seen that a simple ratio existed in this patient on two occasions, although

* Except when the heart is dying or under exceptional experimental conditions, which can hardly be considered comparable to those existing in a relatively healthy patient.

TABLE II. (*Case 1.*)

Number	Intervals between systoles	Intervals between extra-systoles	Number	Intervals between systoles	Intervals between extra-systoles	Number	Intervals between systoles	Intervals between extra-systoles	Number	Intervals between systoles	Intervals between extra-systoles
1			28			56			84		
2	39	59	29	41	61	57	41	61	85	78	
3	20	18* 3 (+5)	30	20	18 × 3 (+7)	58	20	18 × 3 (+7)	86	41	61 3
4	18		31	18		59	18		87	20	18 × 3
5	39	58	32	18		60	18		88	18	
6	19	18 × 3 (+4)	33	41	60	61	23		89	40	61
7	18		34	19	18 × 3 (+6)	62	41	60	90	21	18 × 3 (+7)
8	41	60	35	18		63	19	18 × 3 (+6)	91	18	
9	19	18 × 3 (+6)	36	40	60	64	18		92	42	62 3
10	18		37	20	18 × 3 (+6)	65	40	59	93	20	18 × 3 (+8)
11	41	61	38	18		66	19	18 × 3 (+5)	94	18	
12	20	18 × 3 (+7)	39	41	61	67	18		95	40	60 3
13	18		40	20	18 × 3 (+7)	68	40	60	96	20	18 × 3 (+6)
14	40	59	41	18		69	20	18 × 3 (+6)	97	18	
15	19	18 × 3 (+5)	42	41	60	70	18		98	41	62
16	18		43	19	18 × 3 (+6)	71	40	60	99	21	18 × 3 (+8)
17	40	61	44	18		72	20	18 × 3 (+6)	100	18	
18	21	18 × 3 (+7)	45	41	62	73	18		101	42	62 3
19	17		46	21	18 × 3 (+8)	74	41	60	102	20	18 × 3 (+8)
20	41	60	47	18		75	19	18 × 3 (+6)	103	18	
21	19	18 × 3 (+6)	48	41	61	76	18		104	18	
22	18		49	20	18 × 3 (+7)	77	41	62	105	41	61
23	41	60	50	18		78	21	18 × 3 (+8)	106	20	18 × 3 (+7)
24	19	18 × 3 (+6)	51	40	60	79	18		107	18	
25	18		52	20	18 × 3 (+6)	80	42	61	108	42	62 3
26	40	60	53	18		81	19	18 × 3 (+7)	109	18	
27	20	18 × 3 (+6)	54	40	61	82	18		110	18	
	17		55	21	18 × 3 (+7)	83	39	59			
				17			20	18 × 3 (+5)			

* This figure 18 is an approximate average of all the short inter-extra-systolic intervals of the table.

TABLE III.

Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles
1			28			56		
2	18		29	43	65	57	17	
3	41	64	30	22	18 × 4 (-7)	58	43	65
4	23	18 × 4 (-8)	31	18		59	22	18 × 4 (-7)
5	17		32	43	65	60	18	
6	41	64	33	22	18 × 4 (-7)	61	20	
7	23	18 × 4 (-8)	34	18		62	41	65
8	18		35	43	65	63	22	18 × 3 or 4 (+ or -9)
9	41	63	36	22	18 × 4 (-7)	64	17	
10	22	18 × 4 or 5 (-9)	37	18		65	43	66
11	17		38	43	66	66	23	18 × 4 (-6)
12	41	64	39	22	18 × 4 (-6)	67	18	
13	23	18 × 4 (-8)	40	17		68	42	64
14	17		41	43	65	69	22	18 × 4 (-8)
15	41	63	42	22	18 × 4 (-7)	70	17	
16	22	18 × 3 or 4 (-9)	43	17		71	18	
17	17		44	19		72	42	64
18	19		45	43	65	73	22	18 × 4 (-8)
19	22		46	22	18 × 4 (-7)	74	18	
20	39	61	47	17		75	41	62
21	22	18 × 3 (-7)	48	42	64	76	21	18 × 3 (+8)
22	18		49	22	18 × 4 (-8)	77	18	
23	42	64	50	17		78	42	64
24	22	18 × 4 (-8)	51	19		79	22	18 × 4 (-8)
25	17		52	41	63	80	18	
26	42	64	53	22	18 × 3 or 4 (+ or -9)	81	42	64
27	22	18 × 4 (-8)	54	18		82	22	18 × 4 (-8)
	17		55	42	65		17	
				23	18 × 4 (-7)			

* This figure 18 is an approximate average of all the short inter-extrasystolic intervals

(Case 1.)

Number.	Intervals between successive beats	Intervals between extrasystoles.	Number	Intervals between successive beats	Intervals between extrasystoles.	Number	Intervals between successive beats	Intervals between extrasystoles.
83			111			139		
84	42 } 22 }	64 18 × 4 (-8)	112	42 } 23 }	65 18 × 4 (-7)	140	43 } 21 }	64 18 × 4 (-8)
85	18		113	17		141	18	
86	42 } 22 }	64 18 × 4 (-8)	114	43 } 23 }	66 18 × 4 (-6)	142	44 } 21 }	65 18 × 4 (-7)
87			115			143		
88	17		116	18		144	18	
89	41 } 22 }	63 18 × 3 or 4 (+ or -9)	117	18		145	44 } 22 }	66 18 × 4 (-6)
90			118	43 } 23 }	66 18 × 4 (-6)	146		
91	17		119			147	18	
92	41 } 21 }	62 18 × 3 (+8)	120	17		148	23	
93			121	42 } 22 }	64 18 × 4 (-8)	149	20	
94	18		122			150	43 } 20 }	63 18 × 3 or 4 (+ or -9)
95	41 } 21 }	62 18 × 3 (+8)	123	18		151		
96			124	42 } 22 }	64 18 × 4 (-8)	152	18	
97	18		125			153	43 } 20 }	63 18 × 3 or 4 (+ or -9)
98	41 } 23 }	64 18 × 4 (-8)	126	17		154		
99			127	19		155	18	
100	18		128	42 } 22 }	64 18 × 4 (-8)	156	45 } 22 }	67 18 × 4 (-5)
101	41 } 23 }	64 18 × 4 (-8)	129			157		
102			130	18		158	17	
103	18		131	22		159	44 } 22 }	66 18 × 4 (-6)
104	43 } 23 }	66 18 × 4 (-6)	132			160		
105			133	40 } 21 }	61 18 × 3 (+ 7)	161	18	
106	17		134			162	19	
107	19		135	18		163	43 } 22 }	65 18 × 4 (-7)
108	43 } 22 }	65 18 × 4 (-7)	136	41 } 22 }	63 18 × 3 or 4 (+ or -9)	164		
109			137			165	18	
110	17		138	18		166		

of the table.

TABLE IV.

Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles
1	19		34	19		66	36	55	99	39	
2	17		35	34	52	67	19	18 × 3 (+1)	100	18	57 18 × 3 (+3)
3	18		36	18	18 × 3 (-2)	68	17		101	17	
4	37	56 (+2)	37	17		69	18		102	19	
5	19	18* 3 (+2)	38	18		70	18		103	35	53 18 × 3 (-1)
6	16		39	36		71	36	54 18 × 3	104	18	
7	19		40	18	54 18 × 3	72	18	18 × 3	105	18	
8	35	55 18 × 3 (+1)	41	18		73	17		106	19	
9	20		42	18		74	39	57 18 × 3 (+3)	107	19	
10	16		43	35	54 18 × 3	75	18		108	36	55 18 × 3 (+1)
11	17		44	19		76	17		109	19	
12	36	55 18 × 3 (+1)	45	17		77	40	57 18 × 3 (+3)	110	17	
13	19		46	17		78	17		111	39	57 18 × 3 (+3)
14	16		47	36	54 18 × 3	79	18		112	18	
15	19		48	18		80	18		113	17	
16	19		49	17		81	34	52 18 × 3 (-2)	114	17	
17	36	55 18 × 3 (+1)	50	18		82	18		115	35	53 18 × 3 (-1)
18	19		51	36	54 18 × 3	83	18		116	18	
19	1		52	18		84	18		117	17	
20	39	57 18 × 3 (+3)	53	17		85	18		118	19	
21	18		54	18		86	35	54 18 × 3	119	18	
22	16		55	35	54 18 × 3	87	19		120	36	55 18 × 3 (+1)
23	19		56	19		88	16		121	19	
24	34	53 18 × 3 (-1)	57	17		89	19		122	17	
25	19		58	19		90	19		123	39	57 18 × 3 (+3)
26	16		59	19		91	37	57 18 × 3 (+3)	124	18	
27	39	57 18 × 3 (+3)	60	19		92	20		125	18	
28	18		61	36	54 18 × 3	93	17		126	18	
29	17		62	18		94	19		127	36	55 18 × 3 (+1)
30	17		63	17		95	18		128	19	
31	37	55 18 × 3 (+1)	64	20		96	36	54 18 × 3	129	18	
32	18		65	19		97	18		130	18	
33	17					98	17		131	19	

* This figure 18 is an approximate average of all the short inter-extrasystolic intervals.

(Case 1.)

Number.	Intervals between successive heartbeats.	Intervals between extrasystoles.	Number.	Intervals between successive heartbeats.	Intervals between extrasystoles.	Number.	Intervals between successive heartbeats.	Intervals between extrasystoles.	Number.	Intervals between successive heartbeats.	Intervals between extrasystoles.
132			164			197			230		
133	35 } 19 }	54 18 × 3	165	36 } 19 }	55 18 × 3 (+1)	198	16 38 }		231	19	
134	16		166	17		199	19 }	57 18 × 3 (+3)	232	19	
135	20		167	18		200	17		233	36 } 18 }	54 18 × 3
136	19		168	35 } 20 }	55 18 × 3 (+1)	201	18		234	17	
137	36 } 19 }	55 18 × 3 (+1)	169	16		202	19		235	38 }	55 18 × 3 (+3)
138	17		170	18		203	36 }	54 18 × 3	236	19 }	
139	38 } 18 }	54 18 × 3	171	36 } 19 }	55 18 × 3 (+1)	204	17		237	17	
140	16		172	17		205	19 }		238	19	
141	19		173	18		206	35 }	54 18 × 3	239	18	
142	37 } 19 }	56 18 × 3 (+2)	174	36 } 19 }	55 18 × 3 (+1)	207	19		240	35 }	54 18 × 3
143	17		175	17		208	17		241	19 }	
144	35 }	54 18 × 3	176	18		209	19 }		242	17	
145	19		177	36 } 19 }	55 18 × 3 (+1)	210	16		243	19	
146	18		178	17		211	58 }	57 18 × 3 (+3)	244	19	
147	36 }	56 18 × 3 (+2)	179	18		212	19 }		245	35 }	54 18 × 3
148	17		180	19		213	16		246	19 }	
149	19		181	36 } 18 }	54 18 × 3	214	19		247	17	
150	16		182	17		215	37 }	56 18 × 3 (+2)	248	19 }	56 18 × 3 (+2)
151	20		183	18		216	19 }		249	38 }	57 18 × 3 (+3)
152	19		184	36 } 18 }	55 18 × 3 (+2)	217	16		250	17	
153	37 }	56 18 × 3 (+2)	185	17		218	19 }		251	18	
154	16		186	19		219	38 }	57 18 × 3 (+3)	252	19 }	
155	38 }	58 18 × 3 (+4)	187	18		220	19 }		253	17	
156	20 }		188	36 } 18 }	54 18 × 3	221	18		254	18	
157	17		189	17		222	19 }		255	19	
158	18		190	18		223	37 }	55 18 × 3 (+1)	256	36	
159	36 }	55 18 × 3 (+1)	191	19		224	18		257		
160	19 }		192	36 } 19 }	55 18 × 3 (+1)	225	17				
161	17		193	18		226	37 }	55 18 × 3 (+1)			
162	18		194	17		227	18 }				
163			195	36 }		228	19 }				
			196	19 }		229	18				

TABLE V.

Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles
1			26			51		
2	17		27	18		52	18	
3	17		28	42		53	17	
4	17		29	30	122 17×7 (+3)	54	42	
5	18		30	31		55	32	
6	17		30	19		56	31	185 17×11 (-2)
7	18		31	17		57	31	
8	38		32	17		58	31	
9	30		33	42		59	18	
10	30		34	31		60	18	
11	31		35	32	188 17×11 (+1)	61	17	
12	32	321 $17* \times 19$ (-2)	36	32		62	17	
13	34		37	32		63	17	
14	36		38	19		64	17	
15	37		39	18		65	17	
16	35		40	17		66	17	
17	18		41	44		67	17	
18	18		42	31		68	17	
19	17		43	32		69	17	
20	44		44	33		70	17	
21	32		45	34	327 17×19 (+4)	71	17	
22	32	189 17×11 (+2)	46	34		72	17	
23	31		47	34		73	32	
24	31		48	34		74	32	
25	19		49	33		75	30	324 17×19 (+1)
	18		50	18		31	31	

* This figure 17 is an approximate average of all the short inter extrasystolic intervals

(Case 2.)

Number.	Intervals between successive beats.	Intervals between extrasystoles.	Number.	Intervals between successive beats.	Intervals between extrasystoles.	Number.	Intervals between successive beats.	Intervals between extrasystoles.
76	31		101	31		126	18	
77	31		102	32		127	18	
78	33		103	34		128	17	
79	34		104	23		129	42	
80	23		105	16		130	31	
81	17		106	17		131	30	155
82	19		107	18		132	30	17 9
83	17		108	17		133	22	(+ 2)
84	17		109	17		134	17	
85	17		110	18		135	18	
86	22		111	17		136	17	
87	24		112	18		137	17	
88	38		113	17		138	17	
89	36		114	18		139	17	
90	33		115	18		140	17	
91	32	220	116	36		141	18	
92	31	17×13	117	31		142	17	
93	31	(-1)	118	31		143	17	
94	19		119	31		144	17	
95	18		120	31		145	18	
96	33		121	32	339	146	44	
97	33		122	33	17×20	147	30	
98	30		123	33	(-1)	148		
99	30		124	32				
100	30	276	125	31				
		17×16						
		(+ 4)						

of the table.

TABLE VI.

Number.	Intervals between successive beats	Intervals between extrasystoles	Number.	Intervals between successive beats	Intervals between extrasystoles	Number.	Intervals between successive beats	Intervals between extrasystoles	Number.	Intervals between successive beats	Intervals between extrasystoles
1			35			69			103		
2	16		36	25	353 16×22 (+1)	70	26		104	16	
3	37		37	26		71	26		105	16	
4	27		38	25		72	26		106	23	
5	27		39	26		73	27	416 16×26	107	31	
6	26		40	26		74	26		108	26	
7	26		41	25		75	26		109	26	
8	25	²⁸⁸ $16* \times 18$	42	26		76	25		110	25	
9	26		43	16		77	26		111	25	
10	26		44	17		78	26		112	26	
11	26		45	16		79	27		113	26	
12	26		46	16		80	25		114	25	
13	16		47	16		81	16		115	26	461 16×29 (-3)
14	17		48	36		82	17		116	26	
15	16		49	27		83	16		117	25	
16	16		50	26		84	16		118	27	
17	17		51	27		85	16		119	25	
18	16		52	25		86	36		120	26	
19	36		53	27		87	27		121	27	
20	26	¹⁰⁵ 16×7 (-7)	54	26	393 16×25 (-7)	88	26	157 16×10 (-3)	122	26	
21	27		55	26		89	26		123	26	
22	16		56	27		90	26		124	17	
23	17		57	25		91	16		125	16	
24	16		58	26		92	18		126	16	
25	16		59	27		93	16		127	16	
26	17		60	26		94	16		128	34	51 16×3 (+3)
27	16		61	26		95	16		129	17	
28	23		62	16		96	34		130	16	
29	24		63	17		97	27		131	16	
30	30		64	16		98	25		132	16	
31	26		65	16		99	26	178 16×11 (+2)	133	16	
32	26		66	35		100	25		134	17	
33	26		67	26		101	26		135	16	
34	25		68	27		102	15			16	
	25			26			18				

* This figure 16 is an approximate average of all the short inter-extrasystolic intervals of the table.

(Case 2.)

Number.	Intervals between successive beats	Intervals between extrasystoles	Number.	Intervals between successive beats	Intervals between extrasystoles	Number.	Intervals between successive beats	Intervals between extrasystoles	Number.	Intervals between successive beats	Intervals between extrasystoles
136	35	129 16×8 (+1)	170	26	135 16×8 (+7)	204	26	333 16×21 (-3)	238	17	203 16×13 (-5)
137	27		171	16		205	18		239	35	
138	26		172	19		206	19		240	26	
139	26		173	16		207	16		241	25	
140	15		174	16		208	16		242	26	
141	19		175	16		209	34		243	25	
142	16	98 16×6 (+2)	176	36	103 16×6 (+7)	210	25	55 16×3 (+7)	244	25	222 16×14 (-2)
143	21		177	27		211	26		245	25	
144	21		178	26		212	25		246	16	
145	30		179	26		213	26		247	17	
146	26		180	20		214	26		248	16	
147	26		181	16		215	25		249	16	
148	16	515 16×32 (+3)	182	16	99 16×6 (+3)	216	26	106 16×7 (-6)	250	22	106 16×7 (-6)
149	16		183	16		217	25		251	30	
150	16		184	16		218	26		252	25	
151	16		185	35		219	26		253	25	
152	32		186	27		220	26		254	26	
153	26		187	26		221	17		255	25	
154	26	152 16×9 or 10 (+ or -8)	188	15	152 16×9 or 10 (+ or -8)	222	16	152 16×9 or 10 (+ or -8)	256	25	152 16×9 or 10 (+ or -8)
155	26		189	19		223	16		257	26	
156	25		190	16		224	16		258	25	
157	26		191	21		225	17		259	15	
158	26		192	20		226	37		260	17	
159	26		193	31		227	18		261	16	
160	26	152 16×9 or 10 (+ or -8)	194	26	152 16×9 or 10 (+ or -8)	228	16	152 16×9 or 10 (+ or -8)	262	16	152 16×9 or 10 (+ or -8)
161	26		195	25		229	16		263	16	
162	26		196	17		230	16		264	16	
163	26		197	17		231	17		265	16	
164	26		198	17		232	17		266	36	
165	26		199	16		233	17		267	27	
166	26	152 16×9 or 10 (+ or -8)	200	16	152 16×9 or 10 (+ or -8)	234	16	152 16×9 or 10 (+ or -8)	268	26	152 16×9 or 10 (+ or -8)
167	26		201	32		235	17		269	17	
168	26		202	25		236	17		270	17	
169	26		203	26		237	16				
	26			25			16				

TABLE VII. (Case 2.)

Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles	Number	Intervals between successive beats	Intervals between extrasystoles
1			25			49			73		
2	16		26	31		50	16		74	27	
3	16		27	27	100 16 6 (+4)	51	16		75	26	
4	32		28	26		52	16		76	27	
5	26		29	16		53	33		77	27	
6	26	152 16×9 (+8)	30	16		54	28		78	16	
7	26	16 \times 10 (-8)	31	16		55	27	184 16×11 (+8) or 16×12 (-8)	79	17	
8	16		32	35		56	26		80	16	
9	16		33	27		57	27		81	17	
10	16		34	27		58	27		82	16	
11	16		35	27	182 16×11 (+6)	59	16		83	39	
12	16		36	26		60	20		84	28	
13	32		37	26		61	17		85	28	167 16×10 (+7)
14	26		38	26		62	17		86	28	
15	26	152 16×9 (+8) or 16×10 (-8)	39	17		63	17		87	16	
16	26		40	16		64	17		88	18	
17	16		41	16		65	38		89	16	
18	16		42	33		66	28		90	17	
19	15		43	27		67	27		91	16	
20	16		44	27	184 16×11 (+8) or 16×12 (-8)	68	26		92	17	
21	16		45	27		69	26		93	21	
22	16		46	27		70	27	376 16×23 (+8) or 16×24 (-8)	94	35	
23	16		47	27		71	27		95	28	
24	21		48	16		72	27		96	26	

* This figure 16 is an approximate average of all the short inter-extrasystolic intervals of the table.

on these occasions the rate of beating was not quite the same. Was the simple ratio present on all occasions, and under all circumstances? The answer is in the negative. Five minutes after the curve measured in Table I was taken, the curves measured in Table II were obtained, and fifteen minutes later still, those illustrated by Table III and Fig. 2 were taken.

In Table II, as compared with Table I, the long inter-extrasystolic intervals have lengthened materially, this lengthening being due to delay in the appearance of the normal beat of the auricle following each group of extrasystoles, and being accounted for by a slight decrease in the rate of the sinus rhythm. On the contrary, such change as there is in the short extrasystolic intervals is in the direction of shortening. As a consequence of these rate changes the simple mathematical relation between long and short inter-extrasystolic intervals becomes imperfect, the error averaging 6.5 fiftieths of a second and being always in one direction. In the second curve (Table III) this error has increased further, so that now the long inter-extrasystolic interval deviates from 3 times the mean of the short inter-extrasystolic intervals by an average of 7.6 fiftieths of a second. In other words, the position at which the first extrasystole, following a long hiatus, is calculated to occur, falls almost exactly between two actual extrasystoles (see Fig. 2). The evidence in this table is decisive against the view that in this patient a simple rhythm underlay the extrasystoles.

An examination of Tables I, II and III, compiled from curves taken in this order, makes it obvious that the simple relation between the extrasystolic intervals in Table I was of a purely accidental kind, depending upon the fact that the length of the returning cycles (italicised in the Table) happened to be almost precisely double the length of the preceding cycle (the short inter-extrasystolic). A similar relation is to be found in several of Kaufmann and Rothberger's tables. That the relation was fortuitous in the present case is evident, because it was so readily upset.

Our second observation is of a somewhat different kind. It is illustrated by Fig. 3. For some while this patient has exhibited short paroxysms of tachycardia whose starting point is in the auricle. The end of one paroxysm and the beginning of another is shown in this curve. The usual interval between adjacent paroxysmal beats is 17 fiftieths of a second, and this interval is compared with the long intervals between the end beat of one paroxysm and the first beat of the succeeding paroxysm. In the illustration, this long interval is 324 fiftieths of a second, or almost precisely 19 times the length of the short interval. This strip of curve was taken from a longer one which is tabulated in Table V. In this table the long intervals vary considerably, but each is an almost exact multiple of the basal interval 17. The example is another of a kind used by Kaufmann and Rothberger in support of their theory, and is as convincing as those which they display. But like our last

example its value as evidence is destroyed when, as a result of altering the conditions, the simple ratio is made to vanish. A dose of 1.50 of a grain of atropine given hypodermically led to an acceleration of the heart beat, and curves taken 40 and 55 minutes, respectively, after the injections are tabulated in Tables VI and VII and illustrated by Fig. 4. The ratio of short and long intervals exists over the central portions of the curve (Table VI beats 65-172) without very material error. But at the beginning and ending of the curve, the error becomes so great that the accidental relation in the central portions is at once suggested. That the relation is accidental is confirmed by such a table as the next (Table VII), which is similar to a number taken from the same patient on this and different occasions. In Table VII the multiplication of the basal interval, in this instance 16 fiftieths, brings us to points lying almost midway between the first two beats of each paroxysm.

The conclusion in the case of both examples given is that the establishment of a simple ratio is fortuitous and that such ratios are not long maintained, as they should be if the theory of parasystolic arrhythmias is to hold good.

Each example is comparable to one or more of the seven cases which constitute the evidence of the articles criticised. To bring forward a case which is the counterpart of each of the seven cases in question would be possible perhaps if our observations were extended for a prolonged period of time. But patients in whom complex extrasystolic disturbances occur are not so very common. We have examined 7 such, each on several occasions and, from a total of 92 curves, are able to select only a few out of these in which a simple ratio exists throughout. These curves have come exclusively from the two cases used as illustrations. The proportion would be correspondingly higher had our strips of curve been of shorter duration: in this connection, the fragmentary character of many of the curves published by the authors criticised must be mentioned. The number of curves, and the number of cases, which Kaufmann and Rothberger have been obliged to reject because they fail to show a simple ratio is not known to us, but we gather that in neither instance is the number inconsiderable. When curves of long duration are recorded, the rejections become so numerous, that many patients in whom simple curves present the simple ratio cannot be found. For this reason we content ourselves with the two examples presented and with the criticisms which follow.

To return to Table V: the deviation from a simple multiple of the short interval (17 fiftieths) is here expressed, as in our other tables, by a + or - quantity in the third column. The method of expression used by Kaufmann and Rothberger is a different one. Thus, Table V may be summed up in the two first columns of Table VIII. The expression usually used by Kaufmann and Rothberger is illustrated in the third column.

TABLE VIII.

Long intervals.	1st expression.	2nd expression.
321	$17 \div 19 (-2)$	$19 \div 16.9$
189	$17 \times 11 (+2)$	$11 \div 17.2$
122	$17 \div 7 (+3)$	$7 \div 17.4$
188	$17 \times 11 (+1)$	$11 \div 17.0$
327	$17 \times 19 (+4)$	$19 \div 17.2$
185	$17 \div 11 (-2)$	$11 \div 16.8$
324	$17 \times 19 (+1)$	19×17.0
220	$17 \div 13 (-1)$	$13 \div 16.9$
276	$17 \div 16 (+4)$	16×17.3
339	$17 \times 20 (-1)$	20×16.9
155	$17 \times 9 (+2)$	9×17.2

This second method of expression tends to disperse such error as exists, especially when long intervals are concerned, and thus to conceal the amount of the deviation from the mean value (17.1) when the figures are regarded casually. The display of a large number of apparently simple ratios in Kaufmann and Rothberger's tables, a display which is at first almost convincing, owes not a little to this form of expression.

To exemplify, we take the following summary of one of their illustrative curves (beats 5-165 of the table on page 60 of their paper⁵).

TABLE IX.

Long intervals.	Divisor and dividend.	Long intervals.	Divisor and dividend.
292	$10 \div 29.2^*$	260	$9 \div 28.9$
247	10×29.7	249	$8 \div 31.1$
286	$9 \div 31.8$	314	$10 \div 31.4$
246	$10 \div 29.6$	291	$10 \div 29.1$
309	10×30.9	283	$9 \div 31.4$
244	$8 \div 30.5$	285	$9 \div 31.7$
292	$10 \div 29.2$	280	$9 \div 31.1$
295	$10 \div 29.5$	239	$8 \div 29.9$
293	$10 \div 29.3$	286	$9 \div 31.8$
256	8×32.0		

* In each case these are corrected dividends.

They are dealing with a short inter-extrasystolic interval which averages 30.3 hundredths of a second and with long intervals varying, as the summary shows, from 239 to 314 hundredths of a second. The long intervals are subdivided into 8, 9 or 10 parts and the dividends are all figures which, as the table shows, approach fairly closely to the value 30.3. Examined casually a simple ratio appears to be present; further and more careful examination proves it to be illusory. If we take the dividends 28.9 and 32.0, namely, the extremes of their table, and multiply these by 8, we obtain the figures 231 and 256; it is clear that by using intermediate dividends and multiplying by 8, we can obtain a complete range of numbers from 231 to 256. Similarly, using the same dividends, but multiplying by 9 we can obtain a complete range from 263 to 288; and lastly, multiplying by 10, we can obtain a complete range from 289 to 320. In other words, it is almost a matter of indifference what duration the long inter-extrasystolic interval has, for by choosing a suitable divisor (8, 9, or 10 in the case of intervals ranging from 231 to 320) and allowing the same variation as is shown in the Kaufmann and Rothberger dividends (28.9 and 32.0), we can obtain almost every intermediate figure between 231 and 320. Actually, every intermediate figure is obtained if dividends varying from 28.5 to 32.0 are permitted.

It is but right to state that Kaufmann and Rothberger make use of the method of expression now criticised because they believe that the parasystolic rhythm may itself vary in rate, and that an allowance must be made from time to time for such variations. In point of fact some variations in the rate of this rhythm must be assumed in all Kaufmann and Rothberger's examples: in many of them gross variations must be assumed. Now it is universally recognised that the rates of extrasystolic rhythm arising in the auricle are difficult to influence: they are not affected by posture, respiration or exercise, or are affected in only very minor degree. The relative constancy of extrasystolic rhythms in this respect constitutes one of their most remarkable features. If groups of extrasystoles pertain to a constant extrasystolic rhythm, manifesting itself only by occasional responses of the auricle, then the same constancy of rate would be anticipated as is found in simple paroxysms of auricular tachycardia. Kaufmann and Rothberger point out that variations in the inter-extrasystolic intervals move largely hand in hand with variations in the sinus rhythm intervals, the assumption being that both are influenced and in the same direction by the strength of vagal tone: yet in paroxysmal tachycardia the vagus appears to have little or no influence upon the rate, although its influence may abruptly terminate the paroxysm. When Kaufmann and Rothberger explain the discrepancies in their tables by supposing change in the rate of the parasystolic rhythm, they are again making an assumption which is in conflict with the general evidence. A far simpler explanation of simultaneous increase or decrease in the two series of intervals may be put

forward. Such concordance of rates is found in cases in which the extrasystole is more or less accurately linked or "coupled" to the preceding sinus beat. If we assume that in all instances of coupling, the extrasystole is forced into existence in some fashion by the preceding normal beat, the points at which extrasystoles will occur is controlled by the normal beats and, if the normal beats stand closer together or further apart, there will be corresponding changes in the inter-extrasystolic intervals.

Kaufmann and Rothberger have not entirely neglected to test the effects of altering the sinus rate, and have used atropine and exercise for this purpose. The examples which they give of measured curves, taken before and after atropine, are much too fragmentary to be satisfactory, and even so the examples present notable and unexplained discrepancies. In one example (*Case 3*) of measured curves⁵ taken before and after exercise, the variations in the dividends for both curves are so great as to make the result entirely unconvincing.

It is not possible within the compass of this article to enter into a detailed criticism of all the examples which Kaufmann and Rothberger bring forward in support of their hypothesis: though it is to be understood that none of their illustrations are immune from destructive criticism (see appendix notes). As we have shown, it is possible to bring forward examples in which a simple ratio between long and short inter-extrasystolic interval is to be found: but it can also be shown by longer study of these examples that in them the relation is accidental. Obviously the longer the records measured the less likely is it that this fortuitous relation will be maintained. A main criticism of the curves of Kaufmann and Rothberger is that they are too short, many of them are far too short, to be reliable as evidence. Our point of view is that instances of the simple ratio must be shown in which this is long continued, and continued undisturbed in circumstances in which the sinus rhythm materially alters its rate, thus bringing the conclusions to a severer test; and that unless this can be shown in any given case the hypothesis of parasystole cannot be regarded as applicable to that case.

Lastly, it is to be remembered that the hypothesis put forward, starts under a disadvantage, in that it necessitates a number of pure assumptions, to which we have referred, and which, so it seems to us, are either unsupported by the necessary new evidence or are actually in conflict with present evidence.

Appendix notes.—In studying Kaufmann and Rothberger's paper, I have found on several frequent disagreement with the interpretation of their observations. Thus, on page 47, they forward to support their hypothesis frequently appear to us to do the reverse. Thus the table on page 50 of their fourth article⁶ is notable from this point of view. Atrioventricular extrasystoles are falling at regular intervals after each third normal beat and the inter-extrasystolic intervals are therefore constant. At one point in the middle of table 2, one of 50 beats, an auricular extrasystole occurs and temporarily disturbs the allorhythmia then prevailing; but it is promptly resumed after the disturbance, in precisely its original form. This appears to us to be the expected event, assuming the coupling to depend on the forcing of the extrasystoles by preceding normal beats. Kaufmann and Rothberger explain the resumption of the preceding allorhythmia by assuming that the auricular extrasystole disturbs their parasystolic rhythm,

and disturbs it in such a way that the subsequent coupling is accurately restored. That could only be so if the returning pause of the disturbed parasystolic rhythm were of a precise and critical length; this precise and critical length for the returning pause is accepted by Kaufmann and Rothberger without evidence or apparent hesitation, yet the probabilities against this coincidence are considerable.

2. On two occasions (*Case 1*, Table VII, page 231³, and *Case 4*, page 68⁵) serious discrepancies in the inter extrasystolic intervals are explained by assuming them to be due to lengthening of the conduction intervals between the parasystolic focus and the chamber responding. But, lengthening conduction intervals, as has been pointed out frequently, lead in the human heart to temporary quickening of the rate of the responding chamber. They are not known to produce slowing of the rate, yet it is slowing of the parasystolic rate which Kaufmann and Rothberger are attempting to explain. The scheme given at the top of page 73⁵ is not consistent with our knowledge of block in the human heart.

CONCLUSIONS.

A careful examination of the observations published by Kaufmann and Rothberger in support of their hypothesis, namely, that certain extrasystolic irregularities are produced by the interference of two constantly acting rhythmic centres, and observations of our own upon cases of a similar type, lead us to conclude that the evidence advanced in support of their view is inadequate and that the mechanism of extrasystolic irregularities of this kind has still to be found.

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Fig. 1. A portion of the record from Case 1, from which Table I was constructed. In the and on the successive figure, the normals above the curves are the intervals in 1/100 of a second between the anterior peaks of the extra-systole. The tall vertical lines beneath the curve indicate where the actual extra-systolic peaks fall; the broken lines indicate the points at which extra-systolic peaks originating from the supposed parasyth should occur. Time lines indicate fifths of a second in all curves.



Fig. 2. A portion of a record from the same Case 1, taken 10 minutes later. From this record Table III was constructed.



Fig. 3. A portion of a record from Case 2, from which Table V was calculated.



Fig. 4. A portion of a record from Case 2, taken on the same day, 10 minutes after the one from which Table VII was constructed given hypodermically. From this record Table VII was constructed.

THE IRREGULARITY OF THE VENTRICULAR RATE IN PAROXYSMAL VENTRICULAR TACHYCARDIA.

By G. F. STRONG (Vancouver, B.C.) and S. A. LEVINE (Boston).

(*From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.*)

THE diagnosis of paroxysmal tachycardia can generally be made at the bedside by examination of the heart and by careful consideration of the history of previous attacks determining whether the beginning and ending of the attacks of rapid heart action were abrupt. In a recent publication¹ the regularity of the heart in simple paroxysmal tachycardia was carefully studied and variations in the length of the ventricular cycles were found to be very slight, rarely more than 0.01 of a second. It has been noticed by one of us³ that, although a strikingly constant regularity from beat to beat was present in auricular tachycardia, a slightly irregular rhythm was observed in ventricular tachycardia. This difference is of diagnostic importance because, whereas paroxysmal auricular tachycardia does occur in otherwise normal individuals and may be compatible with a long and useful life, ventricular tachycardia in our experience has always been associated with grave heart disease, especially with coronary sclerosis, and indicates a serious prognosis.

The length of the cardiac cycle in two cases of paroxysmal ventricular tachycardia has been studied. From the electrocardiograms taken during the attack careful measurements were made of consecutive heart cycles. Slight but definite differences were readily seen on ordinary inspection of the heart tracings and slight irregularities were noted with the stethoscope at the bedside. On measuring the heart cycles in the electrocardiograms conspicuous differences in length were readily found in both cases. The records of *Cases 1* and *2* are shown in Figs. 1 to 3. *Case 2*, Figs. 2 and 3, is particularly interesting, in that it showed both the auricular and the

ventricular type of tachycardia. The contrast between the perfectly regular rhythm of the one and the slight but definite irregularity of the other was striking. The variations in the length of the heart cycles even over short periods of several seconds, were 10 to 20 times as great as those usually found in simple paroxysmal tachycardia.¹ Whereas the average variation never reached 0.01 of a second and the maximum variation rarely exceeded 0.01 of a second in auricular tachycardia, the average variation in consecutive beats in these two cases of ventricular tachycardia was 0.025, 0.026, 0.033, 0.080 seconds during various attacks.* (See Table I.)

TABLE I

Case number	Type of tach.	Duration of parox.	Length of heart cycles, in secs.	Maximum variation of entire series.	Maximum variation of two consecutive beats.	Average variation of consecutive beats.
1	Ventricular	2 1/2 days	0.37, 0.365, 0.36, 0.365, 0.37, 0.37, 0.36, 0.35, 0.35, 0.385, 0.435, 0.42, 0.365, 0.46, 0.41, 0.365, 0.35, 0.355, 0.435, 0.43, 0.40, 0.385	0.110	0.095	0.025
1	"	1 hour	0.37, 0.38, 0.36, 0.41, 0.375, 0.375, 0.36, 0.345, 0.33, 0.33, 0.325, 0.35, 0.37, 0.39, 0.38, 0.375, 0.33, 0.34, 0.43, 0.525, 0.355, 0.36, 0.38, 0.355	0.200	0.170	0.026
1	"	4 "	0.33, 0.44, 0.38, 0.345, 0.365, 0.385, 0.36, 0.385, 0.33, 0.295, 0.43, 0.36, 0.36, 0.36, 0.355, 0.365, 0.35, 0.36, 0.355, 0.36, 0.365, 0.37, 0.36, 0.31, 0.38	0.145	0.135	0.033
2	"	Very short	0.305, 0.32, 0.36, 0.32, 0.35, 0.37, 0.285, 0.475, 0.31, 0.48, 0.315, 0.35, 0.34, 0.37, 0.49	0.205	0.190	0.080
2	Auricular	8 hour	0.41, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.41, 0.405, 0.41, 0.41, 0.41, 0.405, 0.41, 0.40, 0.41, 0.405	0.010	0.010	0.003

It is interesting that an example of ventricular tachycardia illustrated in Willius's book on clinical electrocardiography² shows the type of

* A third case (Figs. 4 and 5) is added as a probable instance of ventricular tachycardia. Unfortunately during the normal rhythm no extrasystoles were detected which might have given evidence of the origin of the attack. The same type of irregularity as was found in the other two instances of ventricular tachycardia was present here.

irregularity described in this study. In an article on paroxysmal tachycardia by T. S. Hart², Figs. 7 and 8, which illustrate ventricular tachycardia, show definite irregularity. Further examples of this same mechanism are evident in Plates I, VI, XII in an article by Willius⁶, and in Figs. 7, 9 and 11 in an article by Robinson and Herrmann.⁴

It is necessary to remember that there may be periods during the attack of ventricular tachycardia when the heart action is regular, quite as regular as in the auricular type of tachycardia. But the point that characterizes the ventricular type is that sometime during the attack the rhythm is disturbed appreciably.

It is of some importance to translate the above observations into terms that are applicable in the more ordinary examinations conducted in the sick room. If a patient is in an attack of rapid heart action it is first necessary to determine whether the rhythm is grossly irregular, for if it is, we are dealing with a case of auricular fibrillation. If the rhythm is regular we must listen carefully to detect slight irregularities if possible. If the latter are present the diagnosis of ventricular tachycardia is to be considered, and due regard to this must be given in making a prognosis. If the rhythm is perfectly regular even over long periods of time, *i.e.*, listening for several minutes, we are most likely dealing with a paroxysm of auricular origin, generally auricular tachycardia and rarely auricular flutter. In trying to detect irregularities in ventricular tachycardia one must listen for an appreciable length of time, for the rhythm may be perfectly regular over a certain period and then become slightly irregular, while in auricular tachycardia the rhythm is constantly regular even for hours.

CONCLUSIONS.

The rhythm of the heart in ventricular tachycardia, although fairly regular, shows variations in the length of the cycles that are appreciable, often 0.1 of a second in consecutive cycles, and sometimes as high as 0.19 of a second. The average variation of consecutive beats in the two cases of ventricular tachycardia studied, was over 10 times as great as the average variation in cases of simple paroxysmal tachycardia. The arrhythmia can be detected by auscultation of the heart. It is suggested that this may help to distinguish clinically the ventricular from the auricular tachycardia. This differentiation is important because the prognosis of ventricular tachycardia is always grave while that of auricular tachycardia is not necessarily so.

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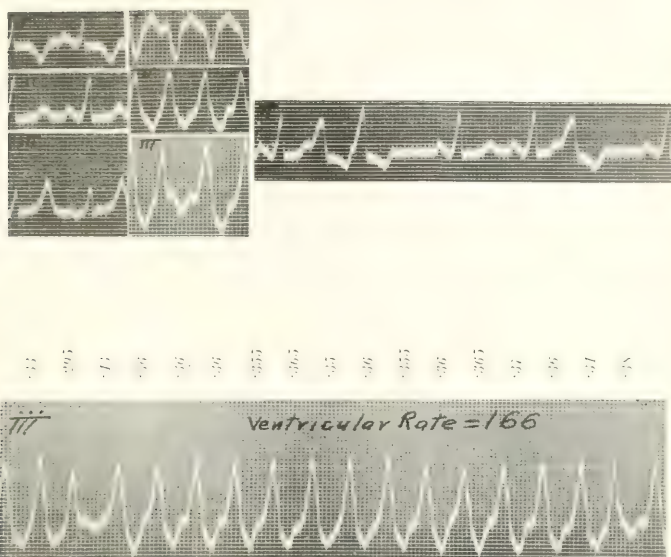


FIG. 1. *Case 1.* Above on the left are curves taken by the three leads on January the 6th, 1920, showing normal rhythm, and those taken on January the 7th, showing tachycardia. On the right is Lead *II* taken on January the 6th and showing three ventricular extrasystoles. Below is—Lead *III* taken on January the 7th and showing tachycardia. Note variations in the length of the inter-ventricular intervals.

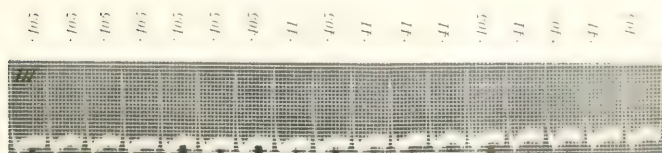


FIG. 2*a*. *Case 2.* Tracing taken on December the 9th, 1916, and showing auricular tachycardia, rate 148. The lengths of inter-ventricular intervals are indicated above the curves. Note the regularity of the auricular tachycardia in Fig. 2*a* and the irregularity of the ventricular tachycardia in Fig. 2*b*.

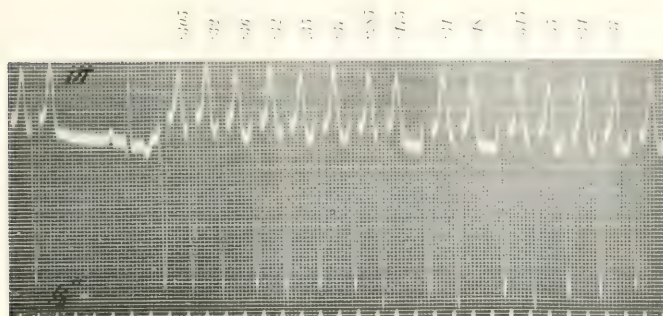


Fig. 2b. Case 2. Taken on December the 11th, and showing a short paroxysm of ventricular tachycardia, rate, approximately, 158.

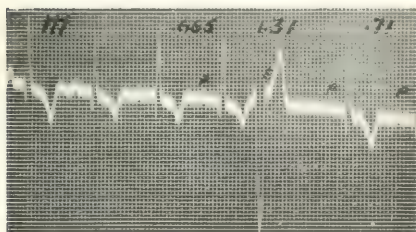


Fig. 3.

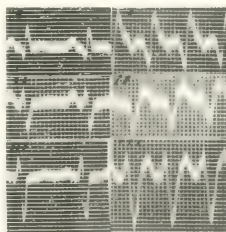


Fig. 4.

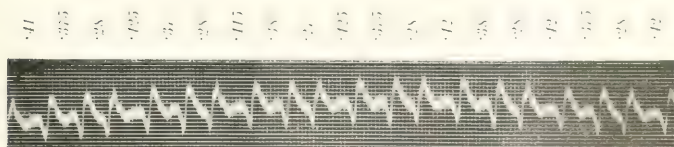


Fig. 5.

Figs. 3, 4, and 5:—Fig. 3. Case 2. Lead III taken on December the 11th, 1916, and showing normal rhythm interrupted by one ventricular extrasystole. Fig. 4. Case 3. Three leads taken on October the 29th, 1916, and showing normal rhythm and those taken on November the 3rd, 1916, and showing tachycardia. Fig. 5. Case 3. Lead I taken on November the 3rd, 1916, during tachycardia. Note variations in the length of inter-ventricular intervals.

THE INFLUENCE OF CIRCULATORY CHANGES ON THE GASEOUS EXCHANGES OF THE BLOOD.

III.—AN EXPERIMENTAL STUDY OF CIRCULATORY STASIS.

By LUCIEN DAUTREBANDE, H. WHITRIDGE DAVIES, and
JONATHAN MEAKINS.

(From the Department of Therapeutics, University of Edinburgh.)

1.—Introductory.

WHILE investigating the blood gases and respiratory function in cases of mitral stenosis, Meakins, Dautrebande and Fetter, whose results appear in a subsequent paper of the present series, found certain anomalies. These authors investigated the carbon dioxide dissociation curves of the blood of such patients, using blood drawn from a superficial arm vein. In addition they investigated the carbon dioxide content of arterial blood, obtained by puncture of the radial artery, as well as the carbon dioxide pressure of the mixed alveolar air to which the blood is exposed in its passage through the capillaries of the lung alveoli. Hence, knowing the carbon dioxide dissociation curve, and the pressure of carbon dioxide to which the arterial blood is exposed in the lungs, the amount of carbon dioxide which should exist in the arterial blood, can be read off from the curve. In normal subjects this amount agrees very closely with that actually found, but in the patients under investigation it was much less. If, however, one calculated the carbon dioxide content of the arterial blood at the existing alveolar carbon dioxide pressure, using the dissociation curve of the blood of a normal subject (that of Haldane³ or either of the present authors, all four of which are in close agreement) it was found that the theoretical amount of carbon dioxide in the arterial blood agreed very closely with that actually found. This fact suggested that the carbon dioxide dissociation curve of blood from a peripheral vein was different from that of the arterial blood, and, moreover, as this anomaly was present only in cases with considerably diminished circulation rate, it appeared probable that local stasis might result in some change which would lower the carbon dioxide combining power of alkaline

reserve") of the blood. The truth of this latter supposition was established by removing the stasis* (immersion of forearm in hot water for about 15 minutes), and in one case by taking arterial blood. It was found that the arterial blood and the venous blood when the arm was placed in hot water showed a carbon dioxide dissociation curve equal to or closely approximating the normal† (Haldane,³ Dautrebande¹, Davies², Meakins²), and, moreover, in each case the arterial carbon dioxide content actually found agreed, within the limits of experimental error (0.5 volume per cent.), with that calculated using such curves.

In order to investigate the means whereby such a change in the carbon dioxide dissociation curve is brought about, it seemed apposite to determine whether such a condition could be produced experimentally by stasis in normal subjects. It was considered possible, in such circumstances, to study the changes in greater detail and thus obtain some more definite idea of their nature.

2. *Production of experimental stasis: symptoms and signs observed. Methods.*

In all four experiments were performed, the duration of the stasis being shown in the results for each experiment (Tables I and II). In the first experiment (that on L. D., Table I, 7.9.22) the stasis was produced by means of a piece of rubber pressure tubing passed twice round the arm and tied so tightly as completely to cut off all circulation, arterial and venous. In the other three experiments the stasis was produced and maintained by means of the pneumatic cuff of a sphygmomanometer, the pressure being kept within 3 mm. () of the observed systolic pressure (125 mm. in the case of H. W. D., and 100 in the case of L. D.). Throughout the whole period there was considerable pain in the region just below that where the pressure was applied. During the first few minutes there were sensations of pins and needles, after which a burning sensation was noticed in the whole forearm, but especially in the distal part. During this period the skin took on a peculiar mottled appearance, with salmon-pink areas of the size of about a centimetre across, enclosed in a reticulum of cyanosis. After about fifteen

* That the stasis was completely removed by this means was shown by the fact that the venous carbon dioxide content and oxygen saturation closely approximated those of arterial blood.

† In the case of H. W. D. and L. D. the determinations of the carbon dioxide dissociation curve have been very complete. In a number of experiments for various purposes we have determined points on these two curves amounting during the last eighteen months to almost fifty in each. In every case the points obtained under normal conditions agreed very closely with those for Haldane's blood. In the original work on Haldane's blood the determinations were made with blood obtained from a finger prick where there was no question of stasis. In our own cases we used venous blood, but always taking care to avoid stasis. We have also found a similar close approximation to Haldane's curve in a number of unpublished observations on patients in whom there is no reason to suspect any abnormality of the carbon dioxide dissociation curve. Hence we are inclined to believe that some at least of the published carbon dioxide dissociation curves which are definitely lower than that of Haldane may be incorrect on account of some local stasis before or when the blood was drawn, and, further, that if one determined the carbon dioxide dissociation curves of a number of normal people under standardised conditions and without exercise or stasis one would find that these curves would approximate very closely to that of Haldane.

minutes (except in the first experiment) definite swelling was apparent, all sensation was lost, and the cyanosis, especially distally, became uniform, and reached its maximum intensity. At this period all power of movement gradually disappeared, the thumb being first paralysed, followed by the forefinger, middle and little fingers, and lastly the ring finger. The forearm and hand remained in this completely "dead" condition throughout the remainder of the period. Complete movement and sensation returned within a few seconds after the constriction was removed. On removing the stasis, a purpuric rash, previously obscured by the cyanosis, became apparent and remained for several days. In the last three experiments no general symptoms were observed, except in the case of H. W. D. (on 11.9.22) when slight chilly sensations were noticed a few minutes after removal of the stasis. In the first experiment on L. D. (7.9.22) all the above symptoms occurred with the exception of the purpuric rash and the swelling.

The blood was drawn from the median basilic vein into a 50 cc. "Record" syringe in which had been placed two or three ccs. of paraffin to prevent contact with air, potassium oxalate to make 0.5 per cent. in the blood in order to prevent clotting, and a trace of sodium fluoride (about 0.1 per cent.) which, as Lovatt Evans¹² has shown, prevents glycolysis and lactic acid formation after the blood has been drawn*. The arterial blood, where required, was obtained by puncture of the radial artery in the manner described by Meakins and Davies.¹³

The carbon dioxide content and the oxygen saturation of the blood were determined by means of the new Haldane blood gas apparatus. Carbon dioxide capacity was determined by the same apparatus, after exposing blood in a saturator at 37°C. to a known partial pressure of carbon dioxide in the manner described by Christiansen, Douglas, and Haldane.³

The pH was not determined directly, but calculated from the ratio combined carbon dioxide, using Hasselbalch's¹⁰ formula, $\text{pH} = \text{pK} + \log \left(\frac{\text{Bik}}{\text{CO}_2} \right)$ free taking 6.1 as the value for pK_a . This formula gives values which are very exact under normal circumstances, but which may be slightly inaccurate under the extreme conditions existing after prolonged stasis. At any rate, the values can be relied on to ± 0.03 .

Blood and plasma chlorides were determined by the method of Wetmore¹⁴ slightly modified in that the amount of blood or plasma used in each determination was estimated by weight and not by volume. We have shown elsewhere¹ that duplicate readings by this method invariably agreed to within one per cent.

Lactic acid was estimated by the method described by Rytzell¹⁵. Haematocrit readings were obtained by using graduated centrifuge tubes, and

* In the experiments shown in Table II fluoride was not added on account of chloride estimation, lactic acid formation being prevented by avoidance of delay in centrifuging the experiment.

TABLE I.

The influence of circulatory stasis upon the carbon dioxide combining power of the venous blood.

Date	Subject	Arterial blood					Venous blood after stasis					Venous blood 30 min in hot water					Remarks
		O ₂ satn. %	O ₂ satn. vol. %	CO ₂ com. vol. %	pH	CO ₂ capacity Vol. %	O ₂ satn. %	O ₂ satn. vol. %	CO ₂ com. vol. %	pH	CO ₂ capacity Vol. %	O ₂ satn. %	O ₂ satn. vol. %	CO ₂ com. vol. %	pH	CO ₂ capacity Vol. %	
7.9.22	L. D.	at 36 mm.					at 40 mm.					at 38 mm.					.1 1/2 hour of stasis. Alveolar CO ₂ = 4.17 % (normal) = 5.40 %
		18.60	99.0	53.4	7.34	51.7	20.80	5.0	66.3	6.80	35.7	18.70	85.0	51.3	7.35	50.0	
11.9.22	H. W. D.	at 37.5 mm.					at 41 mm.					at 40.5 mm.					.1 hour of stasis. Venous blood drawn (at the same time as stasis) from the other arm contained 53.5 vol. % of CO ₂ at 42 mm. of CO ₂ . Alveolar CO ₂ during stasis 5.64 % (normal).
		16.30	98.3	51.5	7.32	49.0	21.33	8.8	58.6	6.79	35.4	16.33	93.3	53.2	7.31	53.0	

centrifugalising the blood under paraffin. Hæmoglobin readings were obtained with the Haldane-Gowers instrument, which has been shown by Meakins and Davies¹³ to be accurate within one per cent., provided sufficient care be taken.

3.—Changes occurring in venous blood after stasis.

The experimental results of all four experiments are shown in Tables I and II. They are best described under six headings :—

(a.) The outstanding feature which occurred in all four experiments was the diminution in carbon dioxide combining power ("alkaline reserve"). Thus

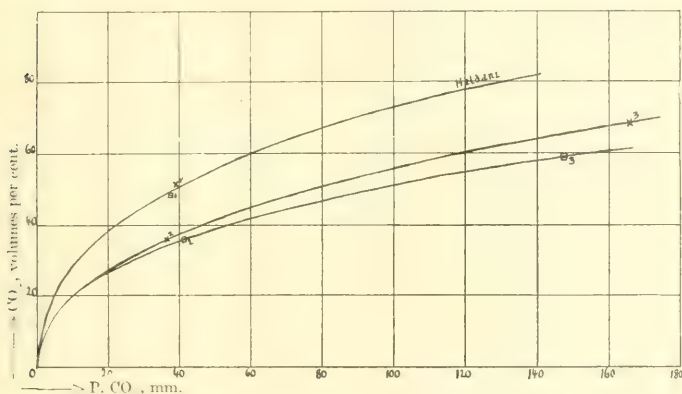


Fig. 1. Stasis experiments :

× = L. D. 7.9.22.

□ = H. W. D. 11.9.22.

1 = CO₂ capacity, normal blood, before stasis.

2 = CO₂ capacity, after stasis.

3 = CO₂ content, venous blood, after stasis.

pH 3 = 6.80.

pH □ 3 = 6.79.

it can be seen from Table I and Fig. 1 that in both subjects the carbon dioxide combining power of blood at 40 mm. carbon dioxide pressure was diminished by 14 volumes per cent.,* representing a diminution of approximately 28 per cent. in "alkaline reserve." The actual carbon dioxide

* By volumes per cent. is meant the number of cc. of gas (corrected to dry volume at standard temperature and pressure) contained in 100 cc. of a given liquid (whole blood, plasma, or corpuscles).

TABLE II.

Comparison of blood drawn from arm when immersed in hot water and during stasis.

Date	S. cell.	CO content of vol. %	pH	CO capacity of vol. %	CO content of plasma vol. %	CO content of cor. vol. %	Leuc. and mm.	Ch. cells, mm. as NaCl	Hb.	Red blood cell.	White cells.	Hema- tocent cells %.	Conditions
								Which present					
							at 41 mm.						
6.10.22	H. W. D.	49.77	7.31	50.20	58.15	31.37	7	47.4	83	4,900,000	6,200	39.3	Arm in hot water.
							at 42 mm.						
		51.22	7.10	44.1	63.0	26.70	8	47.2	106	7,350,000	6,800	44.5	Circulatory stasis (25 minutes).
							at 39 mm.						
10.10.22	L. D.	52.15	7.34	49.5			5*		100				Arm in hot water.
							at 45 mm.						
		54.22	7.10	44.9			6		122				Circulatory stasis (40 minutes).

* At rest for half-an-hour before blood drawn.

content of the blood after stasis did not show more than a slight increase, but in view of the fall in the carbon dioxide dissociation curve (Fig. 1) this represents a great increase in the carbon dioxide pressure of the blood and tissues, amounting to 166 mm. in the case of L. D. and 148 mm. in the case of H. W. D. Consequently the pH of the blood under these circumstances must have been of the order of 6.80 and 6.79, respectively.

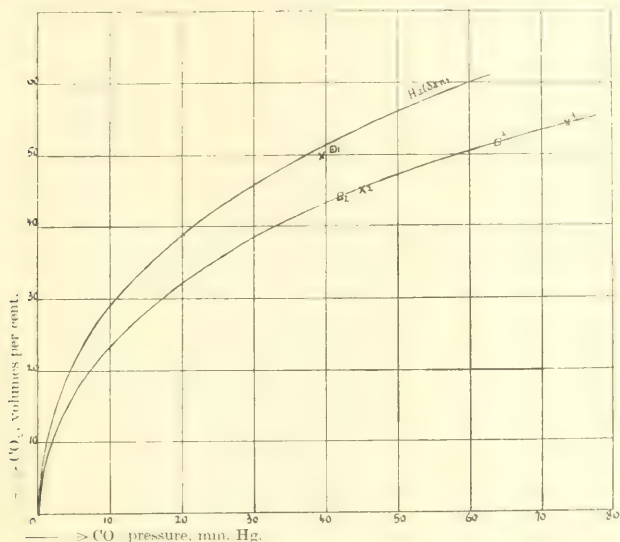


Fig. 2. Stasis experiments:—

□ = H. W. D. 6.10.22.

× = L. D. 10.10.22.

1 = Normal blood before stasis, CO₂ capacity.

2 = CO₂ capacity after stasis.

3 = CO₂ content venous blood, after stasis.

pH = □ 3 = 7.10.

pH = × 3 = 7.10.

In the later experiments, shown in Table II and Fig. 2, these results are confirmed. Here the stasis was of shorter duration and the results more comparable with those found in patients with mitral stenosis. That these manifestations were purely local was shown in the case of H. W. D. (Table I. 11.9.22). Just before the stasis was released blood was drawn from the other arm and showed an absolutely normal carbon dioxide combining capacity. A further interesting fact which may be seen from Table II is

the distribution of carbon dioxide between plasma and cells. Thus before stasis the plasma contained 58.15 volumes per cent. of carbon dioxide, and the corpuscles 31.37 volumes per cent.. After stasis the ratio of volume per cent. in plasma to that in cells was greatly increased, that in the plasma was increased (63.09 volumes per cent.), and that in the cells (26.70 volumes per cent.) was diminished. The increase in the plasma is of interest in view of the reduction of "alkaline reserve." This point is discussed later (page 143).

(b.) The next point of importance was that in all four experiments, there was a considerable concentration of the blood. Thus in Table I, in the case of L. D., the total oxygen capacity increased from 18.60 cc. volumes per cent. to 20.80 cc. volumes per cent., that is to say, the hæmoglobin percentage on the Haldane scale increased from 100 per cent. to 112 per cent.. In the case of H. W. D. the increase was from 16.30 volumes per cent. to 21.33 volumes per cent. (88 per cent. to 115 per cent. hæmoglobin). In Table II these increases may also be seen and in the case of H. W. D. were confirmed by means of red cell count. Thus it is demonstrated that the blood on all four occasions lost on an average approximately twenty per cent. of its water. This water could only have passed to the tissues. With regard to the concentration of the blood, one can readily see from the hæmoglobin and hæmatocrit readings of Table II that, in proportion to its original bulk, the plasma loses about three times as much water as the corpuscles. If one considers what happens to 100 cc. of the original blood of which the hæmoglobin was 83 per cent., it is evident that in order to concentrate this blood to a hæmoglobin percentage of 106, it must have diminished in bulk to $100 \times \frac{83}{106} = 78$ cc., a loss of 22 cc. of water, assuming that all the hæmoglobin remained in the vascular system. Of the original 100 cc., according to the hæmatocrit, 39 cc. were corpuscles. Of the final 78 cc. 44.5 per cent. were corpuscles. Now 44.5 per cent. of 78 cc. is 35 cc.. Therefore what originally was 39 cc. of corpuscles has diminished in bulk to 35 cc.. Therefore, 100 cc. of blood loses 4 cc. of water from its corpuscles, or 10 per cent. of their bulk. If one makes a similar calculation for plasma, it can be seen that the latter loses 30 per cent. of its volume, while each 100 cc. of blood loses 18 cc. of water from its plasma. In making this calculation we have assumed that all the hæmoglobin has remained in the vascular system. This assumption is not strictly warranted, owing to the presence of the purpuric rash. This latter factor, however, would represent such a small proportion of the total hæmoglobin that for practical purposes it can be neglected. Moreover, on no occasion was any hæmoglobinuria observed after these experiments.

(c.) From Table II it can be seen that the chloride *percentage* of the whole blood remained sensibly the same. This fact, taken in conjunction with the loss of fluid from the blood, indicates a loss of chlorides to the tissues. Just as the loss of water was calculated, so also it is possible to say exactly how

much NaCl passed to the tissues. As 100 cc. of original blood contained 474 mg. of NaCl, and as the percentage of NaCl remains sensibly the same after this amount of blood has diminished in bulk to 78 cc., therefore in the 78 cc. of blood there will be $474 \times \frac{78}{100} = 370$ mg. of NaCl. Hence the blood, when it lost 22 cc. of water, also lost 104 mg. of NaCl. That is to say, that the chloride percentage in the escaping fluid $-\left(\frac{104}{22} \times 100 = 473\right)$ is exactly the same as that in the whole blood.

In addition there has been a redistribution of chlorides between the plasma and corpuscles in the blood itself. Thus it can be seen that the chloride percentage in the plasma fell from 591 mg. per cent. to 545 mg. per cent. From these figures, together with the hæmatocrit readings and the percentage of chloride in whole blood, we may calculate the percentages and absolute amounts of chlorides in the corpuscles. As a result of such a calculation we find that during stasis the percentage of chlorides in the corpuscular mass has increased from 292 mg. per cent. to 381 mg. per cent.* We have also seen that what was originally 100 cc. of blood has become 78 cc., and what was originally 39 cc. of corpuscles has become 35 cc.. Now the 39 cc. of original corpuscles contained $39 \times \frac{292}{100} = 114$ mg. of NaCl, while

the final 35 cc. contained $35 \times \frac{381}{100} = 133$ mg. of NaCl. Therefore while from every 100 cc. of original blood 104 mg. of NaCl passed to the tissues, in addition 19 mg. passed from the plasma to the corpuscles. This chloride redistribution in the blood itself is a well-known phenomena *in vitro*, but so far as we are aware it has not hitherto been shown experimentally to occur in the living body. Dautrebande and Davies¹ have elsewhere described experiments concerning this phenomenon, which, as will be seen later, will explain in part the loss of bicarbonate (diminished alkaline reserve) of the blood in conditions of stasis.

(d.) In one experiment (Table I, H. W. D., 11.9.22) the conductivity of the blood serum was measured before and after stasis. We are indebted to Mr. A. R. McLure, of this department, for these measurements. For this purpose special samples of blood were drawn in a syringe without oxalate

* In the blood before stasis let x equal the number of mg. per cent. of NaCl in the corpuscles. Now it was found that in this blood there were 39.3 per cent. of corpuscles and consequently 60.7 per cent. of plasma. The chloride percentage in the plasma was 591 mg., and in whole blood 474 mg. (Table II).

$$\text{Hence } \left(\frac{x}{100} \times 39.3\right) + \left(\frac{591}{100} \times 60.7\right) = 474.$$

Solving this simple equation, we find $x = 292$.

Similarly for blood after stasis—

$$\left(\frac{x}{100} \times 44.5\right) + \left(\frac{545}{100} \times 55.5\right) = 472.$$

$$\therefore x = 381.$$

and without contact with air. The blood was then centrifuged under a layer of paraffin in order to avoid escape of carbon dioxide, and the electrical conductivity of the serum measured at 37°C. This was found in the blood before stasis to be equal to that of an aqueous solution containing 0.66 per cent. of NaCl, while that after stasis was equal to 0.56 per cent. The normal range is from 0.64 to 0.69, hence the serum before stasis was of normal conductivity while after stasis the conductivity was diminished.* This marked diminution of conductivity indicates that the serum has lost salts in greater proportion than it has lost water. And one may justly assume that the loss has not been confined entirely to that of NaCl.

(c.) In order to account for the diminished carbon dioxide combining capacity of blood after stasis, there are two possible explanations.

(1) The presence of a lactic acid acidosis.

(2) The passage from the blood to the tissues of salts, including bicarbonate.

Barcroft and his associates¹ have shown that a lactic acid acidosis may occur in conditions of oxygen want, especially when associated with muscular work. In the present experiments the conditions were those of a severe local asphyxia, and it was considered possible that a lactic acid acidosis might account for some if not all of the diminution of "alkaline reserve." The experiments in Table II, however, show conclusively that this is not so, there being no sensible increase in lactic acid after stasis in either experiment. Such increase as appears (1 mg. per cent.) is within the limits of experimental error, and an increase even greater than this would account only for an infinitesimal proportion of the diminution of "alkaline reserve."

(f.) In addition to the great carbon dioxide acidosis, and the fall in carbon dioxide combining power of the blood it was found after stasis (Table I) that the oxygen desaturation of the blood was extreme. Hence the condition was one of severe local asphyxia.

4.—*Discussion of causes producing blood changes observed during stasis.*

From the experiments described above it has been seen that in local stasis the conditions are those of severe local asphyxia. Associated with this there is a diminished carbon dioxide combining power of the blood (diminished "alkaline reserve"). Moreover, it has been shown that this diminished "alkaline reserve" is not due to a lactic acid (non-gaseous) acidosis. Therefore this diminished alkaline reserve must be due to loss of alkali (bicarbonate) from the blood to the tissues, brought about in some

* Mr. McClure (personal communication) in unpublished observation, has found a lower conductivity in only two cases—that of patients with purpura. In conditions of parenchymatous nephritis with chloride retention the conductivity is increased to considerably above normal limits, readings equal to an aqueous solution of 0.71 to 0.73 per cent. of NaCl being obtained.

way as a result of the extreme carbon dioxide (gaseous) acidosis.[†] Zuntz¹⁷ showed many years ago that when carbon dioxide was added to blood, the plasma, when separated without loss of the gas, was capable of combining with much more carbon dioxide than was the case when the plasma was separated from blood containing little or no carbon dioxide. The interpretation he gave to this phenomenon was that the addition of carbon dioxide brought about a passage of base from corpuscles to plasma. Later, however, Gürber⁷ and others[‡] showed that what really happens is not a passage of alkali from corpuscles to plasma, but a passage of hydrochloric acid in the reverse direction. The carbonic acid, therefore, can displace Cl from dissociated NaCl ions forming bicarbonate and HCl, the latter passing into the corpuscles and combining with the available alkali there, although, as Hamburger⁹ has shown, there is also a slight interchange of cations in addition. Hence it can be seen that at increased carbon dioxide pressures the plasma becomes richer in bicarbonate.

Not only does carbon dioxide displace alkali from the inorganic salts of the blood but in addition it competes with other weak acids for the available alkali. These other weak acids consists of the proteins, hemoglobin and the plasma proteins, which, at the hydrogen ion concentration existing within the physiological range, behave as acids and combine with alkali. Thus we have in blood, outside the body, a system containing a fixed amount of available alkali, and a number of weak acids which vary in amount as Parsons¹¹ has clearly shown.[‡] In the body, however, there is the relationship between the blood and tissues, and what occurs in the latter can be only inferred. We have seen, however, that during stasis the blood loses water, and sodium chloride to the tissues. It appears probable, therefore, that the plasma will also lose other salts, including bicarbonate, in their respective proportions. From the work of Zuntz, Gürber, Hamburger, and others already mentioned, it can be seen that in conditions of asphyxia with a carbon dioxide acidosis the plasma is richer in bicarbonate than normally. That this occurs has already been demonstrated, page 140. Therefore since in such circumstances the blood has lost salts, it seems that it would lose a greater amount of bicarbonate than would occur if the carbon dioxide pressure remained normal. Such a loss would account for the facts we have observed, and would result in a redistribution of salts between the blood and the tissues. This was further indicated by the change in conductivity of the serum.

It is somewhat of an anomaly to find a carbon dioxide acidosis associated with a decreased carbon dioxide carrying capacity. In conditions of chronic carbon dioxide retention, as for example in chronic emphysema, one usually finds an increase of "alkaline reserve." In these conditions, however, the carbon dioxide retention affects the arterial as well as the venous blood, and the increase of alkaline reserve is of the nature of a slowly produced compensatory reaction to a chronic disability.

† For a discussion of this phenomenon, see Dautrebande and Davies.¹

‡ For a review of the carbon dioxide carriers of the blood, see Donald Van Slyke, *Physiological Reviews*, 1921, 1, No. 1.

TABLE III.

The influence of concentration of haemoglobin upon the carbon dioxide capacity of the blood.

Date.	Subject	CO ₂ content of venous blood at 105 mm. Vol. %	CO capacity of normal venous blood at 105 mm. Vol. %	Hb. g.	CO capacity of blood concentrated* at 105 mm. CO pressure	Hb.	Remarks
25.9.22	L.D.	60.72	50.24	101	at 61 mm. 48.00 at 32 mm. 36.00	140	*10 cc. of blood minus 3 cc. of plasma.
23.9.22	H.W.D.	63.5	46.00	94	CO capacity of venous blood centrifuged under paraffin without escape of CO and concentrated* at 37.7 mm. 40.2	142	*10 cc. of blood minus 3 cc. of plasma.
22.9.22	H.W.D.		at 41 mm. 52.2	92	CO capacity of venous blood arterialized and concentrated without precautions for escape of CO at 41 mm. II. 49.00 III. 48.00	112 138	I.—Normal blood. In saturator immediately after blood drawn. II.—Blood centrifuged without paraffin and concentrated 2 cc. of plasma subtracted after centrifugation. III.—Blood centrifuged without paraffin and concentrated. 3 cc. of plasma subtracted after centrifugation. II and III are same sample of blood as I analysed at 1 and 1 hour respectively after I. Glycolysis prevented by fluoride.

5.—*Effects of removal of plasma in vitro.*

In order to test *in vitro* the effect of removal of plasma from blood at various carbon dioxide pressures, the experiments shown in Table III and Fig. 3 were performed. It can be seen that the points for normal blood (column 4, Table III) fell almost exactly upon Haldane's curve (Fig. 3). This

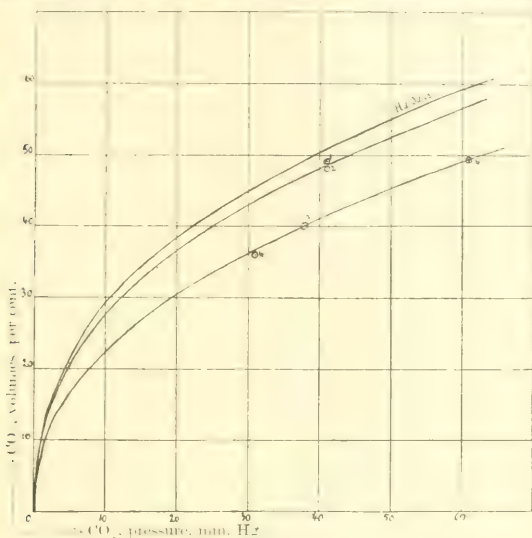


Fig. 3.

Effect of concentration of blood :

1 and 2 = 10 cc. of blood, minus 2 and 3 cc. of plasma, respectively, without precautions for escape of CO_2 .

3 = 10 cc. of blood minus 3 cc. of plasma ; venous blood centrifuged without escape of CO_2 .

4 = Venous blood arterialised, exposed to 105 mm. CO_2 , centrifuged under paraffin and concentrated (10 cc. of blood, minus 3 cc. of plasma).

blood was concentrated in each case by centrifuging for a short time and withdrawing 3 cc. of plasma from each 10 cc. of blood, after which the corpuscles were then shaken up with the remaining plasma. It can be seen (Fig. 3, Nos. 1 and 2) that blood so concentrated at low carbon dioxide pressures loses very little of its carbon dioxide combining capacity, mainly on account of the fact that a large proportion of the available alkali is combined with the hæmoglobin. If, however, one concentrates the blood without allowing escape of carbon dioxide (Fig. 3, No. 3) or after exposing blood to a high pressure of carbon dioxide (Fig. 3, Nos. 4), it can be seen that the effect upon the carbon dioxide combining capacity is comparable to that obtained after stasis. These results are similar to what may be inferred from the results of Joffe and Poulton¹¹.

TABLE IV.
*Capillary carbon tension power of blood as influenced by dialyses against Ringer's and Bayliss-Ringer's
 fluid with and without carbon dioxide*

Date	Subject	I. CO ₂ capacity at 38 mm. normal blood.	II. CO ₂ capacity at 38.4 mm. of blood dialysed against Ringer's solution at 102 mm. CO ₂ and at 37°C.	III. CO ₂ capacity at 34 mm. of blood dialysed against Ringer's solution at 90 mm. CO ₂ and at 37°C.	IV. CO ₂ capacity at 27.5 mm. of blood dialysed against Bayliss- Ringer solution without CO ₂ .	V. CO ₂ capacity at 55.4 mm. of blood dialysed against Ringer's solution without CO ₂ .	VI. CO ₂ capacity at 55.4 mm. of blood dialysed against Ringer's solution without CO ₂ .	After correction for dilution. Standard hemoglobin at 106%					
28.9.22	L.D.	48.7	106	84	31.04	92	27.52	91	31.9.	80	58.3	102	
					35.8		32.05		42.33				

6.—*Dialysis experiments.*

In order to test the effect of changes in carbon dioxide pressure upon the distribution of water and bicarbonate between the blood and a surrounding medium, four experiments were performed. The results are shown in Table IV and Fig. 4. A sample of blood (50 cc.) was drawn from a vein

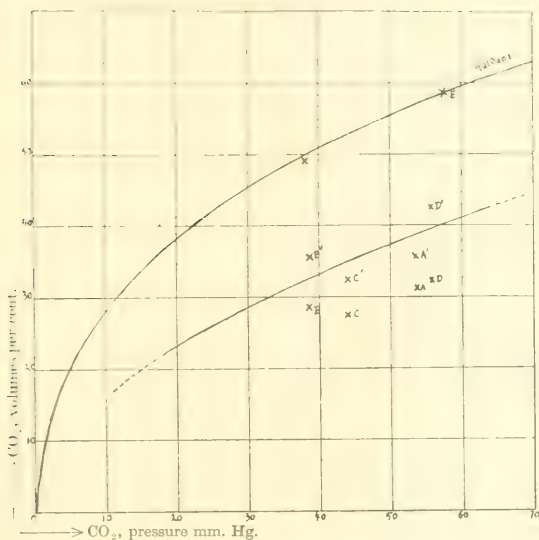


Fig. 4.

Dialysis experiments :

× = Preliminary normal.

A = Blood dialysed against Ringer at 37° C and 90 mm. CO₂ pressure.

B = Blood dialysed against Bayliss gum at 37° and 102 mm. CO₂ pressure.

C = Blood dialysed against Bayliss gum at 37°C and in air.

D = Blood dialysed against Ringer in air.

E = Sample of ordinary blood kept at 37° for same period as A, B, C, D.

A', B', C', D' = A, B, C, D corrected for dilution.

without stasis, into a syringe containing oxalate and sodium fluoride. This was divided into six portions of about 8 cc. each. One was immediately placed in a saturator and its carbon dioxide capacity determined. This was found to be normal (Table IV, column I, Fig. 4, ×).

Four portions were placed in collodion sacs and suspended as follows:

(a) In Bayliss's gum solution, 6 per cent. gum acacia in Ringer's solution (Table IV, column II; Fig. 4, B), with a supernatant atmosphere whose carbon dioxide pressure was 102 mm..

(b) In ordinary Ringer's solution at a carbon dioxide pressure of 90 mm. (Table IV, column III; Fig. 4, A).

(c) Bayliss's gum solution in atmosphere of ordinary air (Table IV, column IV; Fig. 4, C).

(d) Ordinary Ringer's solution in atmosphere of air (Table IV, column V; Fig. 4, B).

All four were placed in a thermostat at 37° C. for slightly more than one hour. At the end of this period the blood was removed from the sacs, and its carbon dioxide combining capacity determined in the usual manner. In no case was there any escape of haemoglobin outwards through the sac, but it can be seen that there was considerable passage of water inwards, as shown by the fall in haemoglobin percentage in each case. In all four experiments there was a marked diminution in carbon dioxide combining capacity. This diminution was greater than could be accounted for by simple dilution with water, as can be seen from A', B', C', D', of Fig. 4, where this factor has been corrected for. Moreover, it is not due to glycolysis, as this was prevented by means of the sodium fluoride, the efficacy of which was demonstrated by keeping an additional portion (No. 6) of the same blood at the same temperature and for the same time, when no such change occurred, as can be seen from Fig. 4, E_x, and Table IV, column VI.

These experiments show conclusively that bicarbonate may pass out from the blood, although the experimental conditions scarcely reproduced those occurring in the living body. The passage of water inwards might be explained on the grounds of the hydrophilic character* of the plasma proteins, or on account of the osmotic pressure of the plasma proteins being greater than that of Bayliss's gum solution. Further experiments along these lines appear to be indicated under conditions which more nearly represent those occurring in the living body.

* An account of the hydration of colloids and a theory of oedema based upon this fact is given by Martin Fischer, "*Oedema and Nephroses*," New York, 1921.

7.—*Discussion. Donnan membrane equilibrium.*

The following schema enables one to obtain some idea of the system with which we are dealing.

<i>Cell interior.</i>		<i>Plasma.</i>		<i>Tissue.</i>
Electrolytes.		Plasma proteins.		Tissue proteins.
H ₂ O, $\frac{1}{2}$ g. H ₂ O.		H ⁺ +		H ⁺
Li		K ⁺		K
K		Na		Na
Na				
Other kations.		Other kations.		Other kations.
OH—		OH—		OH—
HCO ₃ —		HCO ₃ —		HCO ₃ —
Cl—		Cl—		Cl—
SO ₄ —		SO ₄ —		SO ₄ —
Other anions.		Other anions.		Other anions.

Cell membrane.

Vessel wall.

In addition water and some of the electrolytes would be present in their undissociated forms.

Thus we have a system which, for the sake of avoiding undue complexity, we may represent as consisting of three phases separated by two membranes, although the tissues in themselves represent almost an infinity of such phases. With regard to the first two phases—those of the blood itself—the available data are fairly complete, but with regard to the tissues such knowledge as we possess is mainly inferred. Donnan¹² has shown that when a membrane separates two solutions of electrolytes, one of which contains one ion which cannot diffuse through the membrane, the result will be an unequal distribution of the diffusible ions on the opposite sides of the membrane.* This distribution follows definite mathematical laws which can readily be determined for simple systems, and gives rise to changes of potential difference and hydrogen-ion concentration in the various phases of the system.

We are now in a position to discuss what may occur in conditions of asphyxia, such as are present in the tissues in conditions of local and general stasis. In such circumstances, as has been previously mentioned, there exist two conditions, namely, oxygen want, and a great increase in carbon dioxide. The former will disturb the equilibrium of the system by making the hæmoglobin behave as though it were less acid, as had been shown by Christiansen, Douglas and Haldane³ and confirmed by numerous other observers. In addition oxygen want may act by altering the condition of the membranes themselves. The increase of carbon dioxide has the effect of increasing the amount of free (HCO₃) and combined (bicarbonate) carbonic acid present, and indirectly changing the distribution of diffusible ions throughout the entire system. Such a redistribution in the blood itself

* For full discussion of Donnan's Membrane Equilibrium, see Jacques Loeb, "The Theory of Colloidal Behaviour," New York and London, 1922.

results, as we have seen, in a considerable increase of plasma bicarbonate. This in turn would favour the passage of bicarbonate to the tissues. That, however, is not the complete story, for we have yet to explain the passage of water in the same direction. In the dialysis experiments it was seen that water passed into the blood while bicarbonate, and presumably other salts passed out. We feel, however, that the true explanation lies in the water affinities of the various colloids throughout the system. There is no doubt that these would be profoundly modified as a result of the marked changes of pH as shown by Fischer, although he worked with ranges of pH even more extreme than those existing in the blood in our experiments. The pH of the tissues, however, must be much lower than that in the blood, and so, as long as it did not reach the isoelectric point of the tissue colloids, it would definitely increase their hydration.

We have excluded lactic acid as a causative or even contributory factor in the phenomenon of diminished bicarbonate reserve found in stasis. There still remains the possibility of other organic acids being present. In view, however, of the results of our concentration and dialysis experiments, we consider this an unnecessary assumption.

We may conclude then that the diminished bicarbonate reserve in conditions of circulatory stasis is the result of a passage of water together with bicarbonate and other salts from the blood to the tissues. Were the data with regard to the salts, water and colloids of the tissues more complete, it seems probable that the phenomenon would be found to be a "Donnan membrane equilibrium." There is, however, a complicating factor, namely, that the membranes of the system are physiological membranes, consisting of living cells and as such they are profoundly modified by conditions of oxygen want and carbon dioxide acidosis. In this fact we have the probable explanation of the escape of haemoglobin to the tissues as evidenced by the purpuric rash.

It appears that although much work remains to be done in order to explain the details of the phenomenon, our experiments point to a most important factor in the production of oedema in cardiac cases. The theory usually accepted, and based on mechanical and pathological considerations, is that oedema in cardiac patients results from a mechanical squeezing out of fluid from the vessels, brought about by increased venous and capillary pressure. This purely mechanical theory is somewhat unsatisfactory, and, moreover, does not explain many of the facts which we have described above. Such a purely mechanical theory would demand that the composition of the escaping fluid, at any rate as regards salts, would be identical with that of the plasma. It has already been shown that the chloride concentration in the escaping fluid, while equal to that of whole blood, is less than that of the plasma, while in order to account for the diminution of "alkaline reserve," and the great fall in the electrical conductivity of the plasma the bicarbonate concentration in the escaping fluid must have been greater than that of both whole blood and of plasma. These facts can be explained in

the main by Fischer's theory, and completely on the broader basis of the "Donnan membrane equilibrium." The essential factor in such an explanation is the deficient circulation and consequent carbon dioxide acidosis.*

In our experiments the occurrence of gross œdema could not with certainty be observed. Such swelling as occurred during the application of the stasis was mainly of the nature of plethora. In such circumstances the increase of venous and capillary pressure must have been considerable, and hence the absence of gross œdema is in itself an argument against the mechanical pressure theory. On the other hand, the loss of water and salts from the blood must have resulted in a corresponding gain by the tissues and may be accepted as evidence of a certain amount of œdema.† Such œdema would of necessity be limited by the supply of available fluid and salts. Thus it can be seen that the optimum condition for the development of a gross œdema is a circulation so slowed as to result in a carbon dioxide acidosis, but not as slowed as greatly to restrict the supply of available salts and water. We have evidence to show that these conditions occur in most, if not all, cases of circulatory œdema, while the removal of such conditions by increasing the circulation either locally or generally results in the disappearance of œdema.

SUMMARY.

(1) In conditions of stasis the phenomena observed are those of severe local asphyxia.

(2) Under such circumstances the blood becomes concentrated as regards its hæmoglobin percentage. This concentration results from a passage of water from the blood to the tissues. Such passage of water is not entirely due to an increase of venous pressure, as it may occur with the circulation entirely cut off.

(3) There is a passage of chlorides from the blood to the tissues.

(4) The bicarbonate reserve of the blood is lowered. This is not due to a lactic acid acidosis, but is due to passage of bicarbonate from blood to tissues. This has been confirmed in the main by experiments on concentration and dialysis of the blood *in vitro*.

* This conception has, in addition, a wider pathological significance, for it may be possible along similar lines to account for many of the phenomena of inflammation as well as the consolidation and resolution in lobar pneumonia.

† This loss occurred, moreover, in the absence of plethora in the experiments where the arterial supply was completely cut off. Owing to and parallel with the loss of fluid and salts from the blood there must have been a diminution of intra-vascular pressure. This was further emphasized by the great difficulty in obtaining blood from the vein.

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THE INFLUENCE OF CIRCULATORY DISTURBANCES ON THE GASEOUS EXCHANGE OF THE BLOOD.

IV.—THE BLOOD GASES AND CIRCULATION RATE IN CASES OF MITRAL STENOSIS.

By JONATHAN MEAKINS, LUCIEN DAUTREBANDE
and W. J. FETTER.

(*From the Department of Therapeutics, Edinburgh University.*)

Introduction.

THE close association of respiratory symptoms, either subjective or objective, with cardio-vascular lesions has been the subject of many investigations. In fact respiratory disturbances such as cyanosis and dyspnoea have been considered important, if not almost pathognomonic, symptoms in various types of circulatory disturbances. Numerous theories have been put forward to explain their production, but it seems that the problem has always been complicated by the attempt to arrive at a common factor which would explain the occurrence of these and allied symptoms in all lesions of the circulatory system. A systematic investigation of these problems undertaken in this Department soon made it apparent that it was essential that different types of circulatory disturbance should be investigated separately; furthermore, that the cases first investigated should, as nearly as possible, be suffering from a single and well-defined lesion of the circulatory system. It very soon became evident that any attempt to determine the functional disturbances in cases of so-called "decompensated cardiac lesions" were so complicated as to defeat any clear-cut interpretation of their production and of the underlying physiological processes until the individual lesions had been thoroughly investigated. It was found that cases showing signs of gross cardiac failure were subject to so many disturbances of function in different organs that the exact consequences of any single lesion could not be determined. In addition, the respiratory distress in such cases was so acute that many important observations and data could not be obtained. This was particularly so in regard to the alveolar air and the carbon dioxide content of the venous blood which were essential in the

explanation of certain of the physiological disturbances. Animal experiments were found to be unsatisfactory, not only on account of the difficulty of producing lesions similar to those found in man, but also on account of the absence of co-operation by the subject investigated, which is so essential in many of the observations. Therefore it has been necessary to carry out the investigations on human subjects with definite and simple cardio-vascular lesions. It has been found impossible as yet to carry out exhaustive studies on cases with severe cardiac failure. Indeed this has been considered undesirable. The more important period in the progress of these cases is undoubtedly before signs of gross cardio-vascular failure are evident, as it is during this earlier period that the progress of the disease may be influenced. This may be accomplished only if the functional disturbances be understood.

The present communication deals with stenosis of the mitral valve. Five cases have been more or less completely investigated. More cases would have been desirable, but it has been found difficult to obtain cases combining all the factors desired, including sufficient intelligence and co-operation to carry out the simple manipulations oft-times necessary, and absence of other gross lesions. The subjects were comparatively young and free from any other gross organic lesion. For certain reasons some observations have not been possible in two of the cases, in one on account of the removal of the individual from observation, and in the other on account of physical inability to carry out the necessary pulmonary manipulations, due to respiratory distress which rendered the results unreliable.

Summary of cases.

Case I.—H. Age 28. Date of admission: 11/10/21. Weight 47.4 kilog. Height 157 cm..

As a child patient suffered from attacks of pain and swelling in various joints, and on admission had pain and swelling of the left wrist. In October, 1918, following an attack of pneumonia, she developed palpitation and dyspnoea on exertion, which became progressively worse, eventually completely incapacitating her from her work, which was that of a domestic servant.

On examination:—Some clubbing of the fingers; slight cyanosed appearance of the lips and fingers. Pulse 80 per minute, regular in rhythm and force—small volume. The veins of the neck did not show any obvious engorgement. No oedema. Apex beat faintly visible within the nipple line—palpable in the 5th intercostal space and was associated with a definite presystolic thrill. Transverse cardiac dulness—3 cm. to right and 8½ cm. to left of mid sternal line. On auscultation: First sound at the apex was loud and preceded by a short rough presystolic murmur. Second sound reduplicated and followed by a faint diastolic murmur which occupied the greater part of diastole and running into the presystolic murmur. Second sound at the base accentuated and reduplicated particularly in the pulmonary area. Liver and spleen not palpable. On slight exertion in bed pronounced dyspnoea and tachycardia were produced.

30/12/21:—A febrile attack occurred associated with pains and swelling of the joints, which responded to salicylates. Urine was normal. Leucocyte count 8,000.

Diagnosis: Mitral stenosis.

Case II.—B. Age 26. Date of admission: 25/4/22. Weight 44.2 kilog. Height 153 cm..

At the age of 16 patient had growing pains, but was otherwise free from symptoms till the age of 16, when she began to have attacks of precordial pain and palpitation with breathlessness on exertion. During the past ten years she has been in hospital many times on account of severe dyspnoea, palpitation and occasional slight oedema of the ankles. Also on several occasions she has suffered from acute cough with frothy blood-tinged sputum.

On examination: Pulse 74, regular in rhythm and force, small volume, no obvious enlargement of the veins. Apex beat visible in 5th interspace inside the left nipple line. There was a distinct presystolic thrill. On auscultation: rough presystolic murmur heard preceding a loud first sound at the mitral area. Second sound is followed by a very faint diastolic murmur. Second sound at the pulmonary area much accentuated. Liver and spleen not palpable.

Diagnosis: Mitral stenosis.

Case III. M. Age 32. Date of admission: 19/3/22. Weight 49.4 kilos. Height 160 cm.

At the age of 14 patient had acute rheumatic fever, following which she was in bed for six months, and since then she has been subject to acute attacks of vomiting, unrelated to food. These attacks gradually became more frequent and were associated with palpitation. Four months before admission an attack of vomiting occurred similar to previous ones, but associated with very pronounced palpitation and dyspnoea. The vomiting continued at frequent intervals, the palpitation and dyspnoea becoming constant and progressively worse, and slight oedema of the lower extremities developed.

On examination: Pronounced cyanosis with icteroid tinge to the conjunctivæ. Severe orthopnoea with pronounced pulsation in the veins of the neck. Pulse very feeble, 160, irregular both in force and rhythm. Apex beat in 6th interspace $10\frac{1}{2}$ cm. from mid sternal line. No thrill palpable. On auscultation: It was difficult to determine the exact character of the heart sounds on account of the great rapidity and irregularity of the heart.

Diagnosis: Auricular fibrillation.
Mitral stenosis.

On digitalis the patient's pulse was rapidly reduced to between 70 and 80, and all the untoward symptoms disappeared. No engorgement of the veins of the neck. Liver and spleen not palpable. At this time the first sound was very much accentuated, while the second sound was followed by a definite diastolic murmur just inside the apical area. After treatment by quinidine the cardiac rhythm returned to normal.

On examination at this time a pronounced presystolic thrill was evident and also a rough presystolic murmur with a relatively faint diastolic murmur heard best just within the apex area.

Diagnosis: Mitral stenosis.

On discharge patient was quite free of all symptoms and experienced little or no dyspnoea on exertion. After a week's residence at home she had another attack of vomiting and palpitation and pronounced dyspnoea, which necessitated her return to the Infirmary, when the condition was found to be similar to that on first admission after digitalis had been given except that the pulse was more rapid. After another course of quinidine the normal rhythm returned.

Diagnosis: Mitral stenosis.

Case IV. Mc. Age 30. Date of admission: 1/5/22. Weight 47.3 kilos. Height 159 cm.

In 1910 patient had acute rheumatic fever, after which she was quite well until 1919, when she had acute plastic pleurisy. In 1921 she had influenza, and since this time she has been very easily tired and exhausted. On 24/4/22 she was suddenly seized with an attack of vomiting and acute onset of pains in the joints. On 27/4/22 she began to complain of pain in the chest with dry cough, but no sputum. The next day the sputum became copious and was "pink-coloured."

On admission to the infirmary there were signs of broncho-pneumonia and mitral stenosis. There was a considerable degree of cyanosis of the lips, ears and extremities. No oedema. Oxygen was administered at the rate of 1 litre per minute by the Haldane apparatus with disappearance of the cyanosis and great improvement in the patient's condition. She was discharged feeling very well except for some dyspnoea on exertion.

Diagnosis: Mitral stenosis.
Broncho-pneumonia.

19/7/22. Patient readmitted to the Infirmary suffering from extreme breathlessness, swelling of the ankles and acute pains in the joints. On examination: Pulse was 100, regular in time and force. Slight cyanotic appearance of the lips, ears and finger-tips, the latter showing distinct clubbing.

Apex diffusely visible, and there was pronounced pulsation in the veins of the neck and over the liver. The point of maximum pulsation of apex was in the 5th intercostal space $10\frac{1}{2}$ cm. to left of mid-sternal line, accompanied by a presystolic thrill. Auscultation: first sound at the apex sharp and loud and preceded by a short, harsh presystolic murmur. A short distance within the apex area a soft diastolic murmur was heard. In the tricuspid area a blowing systolic murmur was audible which was propagated downwards and to the right. Second pulmonary sound accentuated and reduplicated. Liver palpable and pulsating. The urine contained a small amount of albumen and bile. Lungs were clear.

On rest in bed patient soon improved, but the outstanding features of dyspnoea, weakness and tachycardia on exertion still remained in a comparative degree, no pulsation of the veins of the neck and liver and spleen not palpable.

Diagnosis: Mitral stenosis with cardiac failure.

Case V.—S. Age 45. Date of admission: 21/12/21. Weight 48 kilog.. Height 152.4 cm..

At the age of 27 patient had acute rheumatic fever. After this she was never in perfectly good health, while since the age of 36 she has been definitely incapacitated with cardiac symptoms. These at first were manifested by precordial pain and dyspnoea on exertion. They gradually became worse until a few weeks before admission the breathlessness was extreme and oedema of the legs rapidly developed. She had orthopnoea and inability to walk more than a few steps at a time.

On admission: Pulse regular, 80 per minute. Apex beat 5th intercostal space 9 cm. to left of midsternal line. At the mitral area the first sound was loud and preceded by a short murmur. A few cm. within this area a distinct though faint diastolic murmur was heard. Over both the mitral and the tricuspid areas there was a harsh systolic murmur. Veins of the neck showed very pronounced pulsation. Abdomen was distended with ascites and the liver was palpable and pulsating. Lungs showed a large number of crepitations both anteriorly and posteriorly at the end of inspiration. Electrocardiograph showed a regular rhythm. There was pronounced cyanosis of the lips, ears and extremities.

On rest in bed patient rapidly improved and was discharged in five weeks' time, only to be re-admitted in a fortnight suffering from the same symptoms, from which she made a good recovery. Discharged in five weeks' time.

19.6/22. Patient re-admitted, the condition being identical to that on the previous admissions. Shortly after coming under observation, however, it was noted that the pulse was distinctly irregular, although it had not been so on admission when the electrocardiograph showed normal rhythm. At this time patient's pulse was very rapid and irregular—140, and was counted with great difficulty at the radial artery.

Her condition slowly improved, and at the time of the present observations she was free of oedema, cyanosis, and although she can lie flat in bed she prefers the sitting position, auricular fibrillation persisting.

Diagnosis: Mitral stenosis.
Auricular fibrillation.

Methods.

The alveolar air was determined by the Haldane-Priestley¹¹ technique. Various other methods were tried but with indifferent results. It was not possible at first to obtain satisfactory results in *Case 5* on account of the patient's inability to expire forcibly. At the time, this case suffered from very acute respiratory distress and orthopnoea and inability to hold her breath for more than a few seconds, but as her condition improved, and with persistent training, she was eventually able to deliver very consistent samples of alveolar air.

The expired air and respiratory exchange were estimated by the Douglas bag method. They were not usually determined under "basal conditions" * as it was considered advisable to make as many of the blood and respiratory observations as possible under similar conditions—at rest in bed or in a chair, without previous exercise or a heavy meal. This neglect of basal conditions was necessary because as many observations as possible were made in rapid succession, every precaution being taken to prevent excitement or undue alarm. Frequently a patient was taking part in repeated observations over the greater part of the day, although at no time did fatigue or discomfort

* After twelve hours of fasting and absolute rest in bed.

occur. Many trial tests were introduced as a preliminary to render the subject familiar with the procedure and to avoid emotional disturbances during the real tests. The results of repeated experiments under similar conditions gave remarkably concordant results.

The carbon dioxide and oxyhamoglobin dissociation curves were constructed with every regard to known sources of error. The blood was drawn from the vein with as little stasis as possible into a 50 cc. syringe containing a small amount of neutral potassium oxalate. It was immediately transferred to a large test-tube packed in ice, and sodium fluoride added in sufficient quantity to make a 0.1 per cent. solution. As far as possible the means advocated by Lovat Evans⁹ to prevent glycolysis and acid formation were observed. The blood was used as rapidly as possible, and one portion was not used for more than one observation. Seven cc. of blood were placed in a saturator (400-500 cc. capacity) and sufficient oxygen or carbon dioxide added to make the appropriate partial pressures of gases. The saturator was slowly rotated in a large water bath accurately maintained at 37°C. by electrical means. After five minutes the excess pressure was released and the rotation continued for another ten minutes when samples of blood were removed into accurately calibrated pipettes, every precaution being taken to prevent contamination with air. The percentages of gases in the saturator were analysed in a Haldane gas analysis apparatus. The carbon dioxide content and the oxygen saturation of the blood were estimated with the Haldane blood gas apparatus¹² and, when considered necessary, duplicate observations were made. If the results did not agree closely they were discarded. This was very seldom the case, and was always due to some unavoidable but apparent error of technique.

The arterial blood was obtained according to the usual technique by puncture of the radial artery, the syringe containing neutral potassium oxalate and liquid paraffin to prevent clotting and contamination with air. In cases of mitral stenosis, where the pulse is small and particularly when irregular due to auricular fibrillation, this is difficult. Persistence and care of minor details made it possible in all the cases attempted. *Case 1* had disappeared from observation before the necessity of examining the arterial blood was appreciated.

The circulation rate was determined by the method of Meakins and Davies¹⁵. The results under similar conditions agreed very closely. As will be pointed out subsequently, the values of the carbon dioxide content of the mixed arterial and venous bloods, whether plotted from the carbon dioxide dissociation curve of Haldane³ or of the particular patient in question, made very little difference in the results. Any criticism of this method would indicate that the results for circulation rate obtained in such cases as are at present under consideration, were too high. Under such circumstances it would be reasonable to grant that the results obtained are not as conspicuously low as might be obtained by other methods. A full discussion of the determination of the circulation rate as estimated by the comparison of the

arterial and venous carbon dioxide content and the effect of partially reduced blood upon the carbon dioxide content has been given by Haldane and Douglas⁷.

Gaseous content of venous blood.

The gaseous content of the venous blood from the arm was found to be very variable and dependent on so many factors of external environment that concordant results could not be obtained. Such observations, however, as were made under ordinary conditions substantiated the results of Lundsgaard¹¹. We have shown in previous experiments¹⁶ that the temperature environment of the part from which the venous blood is drawn profoundly influences its gaseous content. In order to overcome such influences we placed the arm from which the venous blood was drawn in as nearly constant surroundings as possible. The hand and fore-arm to the elbow were placed in a water-bath at 45° to 47° C. and retained there for 30 to 40 minutes. Slight pressure by the finger was then exerted over the median basilic or median cephalic vein if necessary, and a needle, attached to a syringe prepared as for arterial puncture, was introduced, and such very small quantity of blood was withdrawn as to indicate that the needle was in the vein. This having been ascertained, the pressure was removed and a few minutes allowed to elapse, the arm remaining in the hot water, before the syringe full of blood was removed. In this manner it was hoped to obtain venous blood free of the effects of stasis. We have previously demonstrated¹⁶ that, by immersing the arm in a water-bath at 45° C. the venous blood of a normal person closely approximates the arterial blood in its gaseous content, this being apparently brought about by the great increase in the rapidity of the blood-flow through the part. In view of this observation on normal people it was obviously important to consider whether similar results would occur in cases of mitral stenosis. In Table I these results are shown.

TABLE I.

Gaseous content of venous blood at constant temperature.

<i>Case.</i>	<i>Temperature.</i>	<i>Oxygen saturation percentage.</i>	<i>Carbon dioxide content volumes percentage.</i>
2	45° C.	94	48
3	47	97	50
4	46	94	44
5	46	91	47

It will be seen that these findings in the venous blood under such special circumstances very closely approximate to those of the arterial blood (Table II). In fact the correspondence is so close that in one instance the venous oxygen saturation is higher than the arterial and the carbon dioxide content is identical. This anomalous result may be explained by the fact that the specimens of blood were withdrawn on different days, and the error of estimation may be considered as ± 0.5 per cent.

The difference between the gaseous content of the venous blood before and after immersion in hot water was very conspicuous. But in view of the observed variations in normal people under similar temperature variations it was not considered that the slightly increased differences in cases of mitral stenosis gave any definite indication as to the circulation as a whole, although it might suggest the possibility of a general circulatory slowing.

Gaseous content of the arterial blood.

In four cases the gases of the arterial blood were determined. In all of them the oxygen saturation closely approximated to the normal. In three of the cases the cardiac rhythm was regular at the time of examination, while in *Case 5* auricular fibrillation was present with a cardiac rate of 130. In none of them were there any signs of pulmonary cedema or other lesions which would interfere with the proper aeration of the venous blood while passing through the pulmonary circulation.* This is in conformity with the results obtained by one of us¹⁷ in cases of auricular fibrillation under similar conditions and in regular and irregular tachycardia in animals with adequate pulmonary ventilation.

TABLE II.
Cases in the arterial blood.

<i>Case.</i>	<i>Date.</i>	Oxygen saturation per cent.	Hb per cent.	Carbon dioxide content volume per cent.
2	15.9.22	98.0	83.0	42.0
3	4.9.22	94.0	83.0	50.0
4	5.9.22	98.0	100.0	42.2
5	6.9.22	96.0	76.0	46.0
Average ..		96.5	85.5	44.0

* In none of the cases, with the exception of *Case 5*, were there any signs of cardiac failure at the time when the recorded observations were made.

Although all of these cases exhibited a more or less pronounced degree of peripheral cyanosis, there was no abnormal oxygen desaturation of the arterial blood. This was the case in spite of the fact that there was very pronounced respiratory distress in all of them on slight exertion and in two (*Case 4*, and particularly *Case 5*) at rest. It was, therefore, considered established that the symptoms experienced in such uncomplicated cases of mitral stenosis were not due to a deficiency in the oxygen saturation of the arterial blood or, in other words, to a true arterial anoxæmia.

The carbon dioxide content of the arterial blood was distinctly below what we had found in many normal cases. But it was found not to be equally

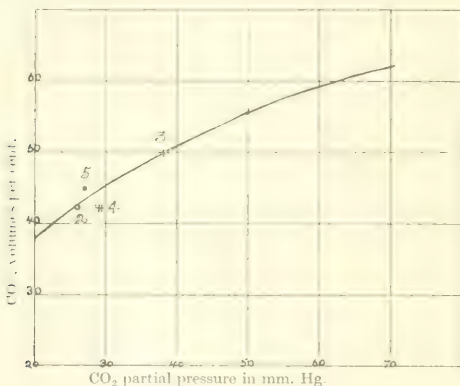


Fig. 1. The carbon dioxide content of the arterial blood, plotted according to carbon dioxide partial pressure of the alveolar air: ○—*Case 2*, —○—*Case 3*, +—*Case 4*, ●—*Case 5*.

lowered in all cases. In the cases with the lower carbon dioxide content there was a higher oxygen saturation. It might be suggested that this condition had resulted from contamination with air at the time of withdrawal of the blood from the artery. However, there was at no time any indication that this had taken place. Another obvious explanation was that there was a considerable increase above normal of pulmonary ventilation in order to reduce the carbon dioxide of the arterial blood for physiological compensatory reasons. This point will be considered subsequently. In addition, such a diminution in the carbon content of the arterial blood might indicate a lowering of the bicarbonate reserve. But on further investigation, this problem threw an important and new light upon the physiological processes present in these cases. In order logically to interpret these results it was necessary to check the findings of the arterial carbon dioxide content,

the carbon dioxide partial pressure in the alveolar air, and the carbon dioxide dissociation curves. It was found that by plotting the carbon dioxide content of the arterial blood with the partial pressure of the mixed alveolar air at the time of observation that they practically coincided with what would be expected (Fig. 1), if the carbon dioxide dissociation curve of the arterial blood closely approximated that of Haldane³. This, however, would not indicate a lowering of the bicarbonate reserve but a reduction of the carbon dioxide content of the arterial blood with a normal bicarbonate reserve: in other words, a gaseous alkalosis in the arterial blood. If this were the case normal carbon dioxide dissociation curves would have been expected. The findings as determined from the ordinary samples of blood from the veins of the arm at first cast doubt on this presumption.

Carbon dioxide dissociation curves.

Numerous points for the carbon dioxide dissociation curves of these patients were determined. It soon became apparent that although a number of estimations determined from one sample of blood gave very consistent results, these were not comparable with the results obtained on another day. In Fig. 2 typical dissociation curves as obtained from single samples of blood are shown. In Fig. 3 the diversity of the findings on different samples of blood is demonstrated. Furthermore, when the carbon dioxide content of the arterial blood was plotted on the carbon dioxide dissociation curves obtained from ordinary venous blood with very slight stasis, they would indicate a carbon dioxide pressure of the mixed alveolar air very much higher than that found at any time in these cases. This would be greatly at variance with the observed findings of the arterial carbon dioxide content and the mixed alveolar carbon dioxide pressures. A comparison of observed and calculated alveolar carbon dioxide partial pressures are given in Table III.

TABLE III.
Comparison of calculated and observed alveolar CO_2 partial pressures.

<i>Case.</i>	Calculated partial pressure of CO_2 in the alveolar air in mm. Hg.	Observed partial pressure of CO_2 in the alveolar air in mm. Hg.	Difference between calculated and observed in mm. Hg.
2	30	27	3
3	47	38	9
4	38	30	8
5	35	27	8

It was considered probable that these variations might possibly be due to inherent differences in the venous blood consequent upon variations in the local circulation. In the preceding paper of this series we have shown the great influence which even temporary circulatory stasis may have upon the carbon dioxide combining power of venous blood. It became apparent, therefore, that the venous blood if used for carbon dioxide dissociation curves should as closely approximate to arterial as possible. The ideal to be attained to of course would be to employ arterial blood in all such observations. But the difficulties of obtaining frequent samples of arterial blood from such cases made this impracticable.

In view of our previous findings that the venous blood withdrawn from the vein of the arm after the latter had been immersed in hot water, closely approximated to the characters of arterial blood, we determined to use such blood for carbon dioxide dissociation curves. A series of observations was carried out with this object in view. All determinations were made in duplicate. Comparative findings in a set of such experiments are given in Table IV. The blood was drawn into a syringe containing a small amount of neutral potassium oxalate and immediately transferred to a saturator containing a partial pressure of carbon dioxide of 40 mm. Hg and over 150 mm. Hg partial pressure of oxygen in order to fully saturate the oxy-haemoglobin. It was but a matter of a few seconds between the withdrawal of the blood from the vein and the immersion of the saturator in the water bath.

TABLE IV.

A comparison between the carbon dioxide combining power of ordinary venous blood and venous blood after the arm has been immersed in hot water.

<i>Case.</i>	CO ₂ content of ordinary venous blood after equilibration with a partial pressure of 40 mm. Hg.CO ₂ *	CO ₂ content of venous blood after arm was immersed in water bath at 45°C. and after equilibration with a partial pressure of 40 mm. Hg.CO ₂ *	
1	47.5		
2	47.5	48.5 48.2	48.3
3	47.0	49.5 50.3	49.93
4	42.5	51.23 50.06	50.65
5	48.0	51.46 50.47	50.97

* The blood was fully oxygenated.

The probable causes of differences observed under such a modification of environment have already been discussed in a previous paper⁵. It appeared to be quite clear that they were due to the passage of bicarbonate from the blood to the tissues.

In view of these findings, and those of the previous paper already referred to, it was considered essential that the carbon dioxide combining power of the venous blood, made as nearly arterial as possible by the application of heat, should be fully determined. This was done, and the results will be found as dotted lines in Fig. 2. It will be noted how closely they approximate

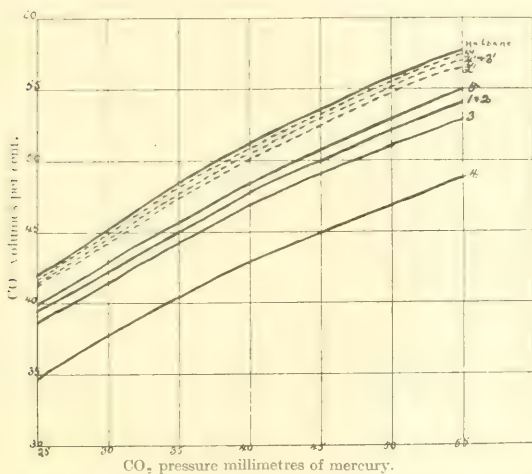


Fig. 2. Carbon dioxide dissociation curves. Curves 1, 2, 3, 4 and 5 are those with ordinary venous blood in Cases 1, 2, 3, 4 and 5. Curves 2', 3', 4' and 5' are those with venous blood obtained from arm in hot water in Cases 2, 3, 4 and 5. Upper curve normal.

to the normal curve as represented by the carbon dioxide curve of Haldane, which is practically identical with the curves of three of us published elsewhere¹⁻⁶. It was considered, therefore, that for all practical purposes the carbon dioxide curves of the arterial blood of these five patients with mitral stenosis might be considered as well within the normal limits. Therefore the depreciation of the carbon dioxide content of the arterial blood could not be considered as due to a lowering of the bicarbonate reserve but rather as a compensatory phenomenon.

The anomalous condition arising from using the carbon dioxide dissociation curves obtained with ordinary venous blood in these cases is

further evident when the pH of the venous and arterial blood were determined.

It has been shown by Fraser, Ross and Dreyer¹⁰ that the reaction of the arterial blood, in cases of cardiac dyspnoea, tends to be more alkaline than in normal subjects. This was particularly evident in cases with signs of cardiac failure. They employed the method described by Dale and Evans¹ for the calorimetric determination of the reaction of the blood by dialysis. We have employed the formulae of Hasselbach,¹³ obtained by comparing the

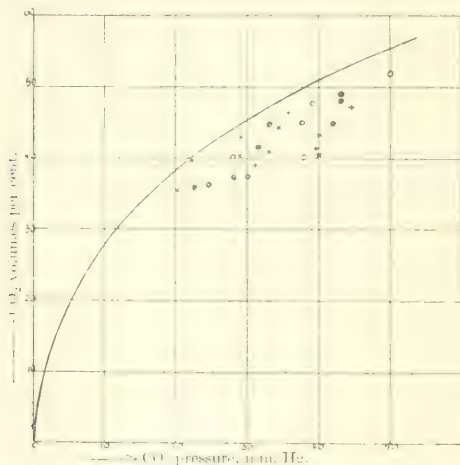


Fig. 3. Points on the CO_2 dissociation curves with different samples of ordinary venous blood. —○— Case 1, —□— Case 2, —△— Case 3, —◇— Case 4, —●— Case 5.

ratio of combined to free carbon dioxide. As has been pointed out by Van Slyke,¹² this method gives a very accurate and consistent estimation of the pH of the blood. The actual findings are not comparable with the method of Dale and Evans, but are proportionately so. Van Slyke found the normal pH of arterial blood as determined by the method of Hasselbach to average 7.33. In Table V will be found the results obtained by this method in the cases here reported. It will be noted that the pH of the arterial blood as determined by the carbon dioxide dissociation curve of arterial blood inclines to an excessive alkalinity (column 3). If, however, the pH of the arterial blood be estimated by using the carbon dioxide dissociation curve of ordinary venous blood it is found to tend more towards an acid reaction (column 1). In order to determine the actual pH of the venous blood in these cases, it is

necessary to use this venous dissociation curve, which indicates that there is a definite difference in the pH between the arterial and venous blood (columns 2, 3 and 5). This variation is more than would be expected under normal conditions. It is evident, therefore, that the general arterial blood has a normal or slightly alkaline pH, while the pH of the venous blood draining the peripheral areas tends to have a relatively lower or more acid pH. The explanation of this condition has been referred to in a previous paper⁵. It is interesting to note that there is a consistent relationship between the increase of the pH in the arterial blood and the relative decrease in the venous blood (Table V) and the decrease in the general circulation rate (Table X).

TABLE V.
pH calculations for rates of *comb. vol.* \times $\frac{1}{\text{rate CO}_2}$.

Subject.	1 Arterial pH calculated, using venous blood dissociation curve	2 Venous pH calculated, using venous CO ₂ dissociation curve.	3 Arterial pH calculated, using arterial CO ₂ dissociation curve.	4 Difference between 1 and 3.	5 Difference between 3 and 2.
1	7.38	7.32	—	—	—
2	7.41	7.35	7.44	0.03	0.09
3	7.32	7.27	7.35	0.03	0.08
4	7.32	7.27	7.40	0.08	0.13
5	7.41	—	7.47	0.06	—

Oxy-haemoglobin dissociation curves.

The oxygen saturation of the arterial blood in these cases of mitral stenosis was within the normal limits of saturation. This might have occurred despite a simultaneous more or less pronounced lowering of the oxy-haemoglobin curve. A number of estimations of the oxygen saturation under known oxygen and carbon dioxide pressures were made on the same sample of blood drawn from the vein and preserved with the precautions as stated above. If all the separate observations in each case did not agree closely, the whole procedure was repeated. This was only necessary in one case and then was found to be due to an obvious error in technique.

The oxy-haemoglobin curves are plotted in Fig. 4 according to the carbon dioxide pressure of the alveolar air present in each case at the time of observation. It will be seen by comparison with the normal limits of oxy-haemoglobin curves that the curves in these cases are in the upper limits

of normality at their own alveolar air carbon dioxide partial pressures. At 40 mm. of carbon dioxide pressure they would occupy an average position in comparison with normal curves. We could find no evidence to indicate that there was any change in the oxy-hæmoglobin curves or in the oxygen tension of the arterial blood that would account for the symptoms of these patients.

Alveolar air.

Some difficulty was encountered at first in each case in obtaining consistent samples of alveolar air. This difficulty was due either to confusion in manipulation or to the difficulty the patient had in expiring deeply (sometimes both factors were operative). With patience and repeated attempts the necessary skill was acquired so that consistent readings were obtained in a large series of observations. The averages of these are found in Table VI.

TABLE VI.
Average alveolar air determinations.

<i>Case.</i>	<i>CO₂ in mm. Hg. average.</i>	<i>Oxygen in mm. Hg. average.</i>	<i>R.Q. average.</i>
1	32.0	—	—
2	27.0	112	0.794
3	{ 39.0 normal rhythm 34.0 aur. fibrillation	{ 106 110 }	0.940
4	29.0	111	0.812
5	27.0	112	0.785

The alveolar air findings in these cases agree with those of Barr and Peters² in that there is a diminution in the carbon dioxide partial pressure. In view of the observations on the carbon dioxide content of the arterial blood this is what would have been expected under the circumstances. A parallelism was found in these cases between the depreciation in the alveolar air carbon dioxide partial pressure and the severity of the symptoms. This is well illustrated in *Case 3*, where the alveolar air carbon dioxide was consistently low during the periods of auricular fibrillation as compared with those during the normal rhythm. As none of the cases here recorded may be classed as having severe cardiac failure, the results are not in some details so conspicuous as others reported. But they have the advantage of being cases in which a clear-cut picture might be expected.

Pulmonary ventilation and basal metabolism.

In view of the lowering of the carbon dioxide partial pressure in the alveolar air and consequent lowering of the carbon dioxide content of the arterial blood it was considered of importance to determine the character of the pulmonary ventilation in these cases. These observations are set forth in Table VII. It will be noted that under resting conditions the respiratory rate is usually in the upper limits of normality. The total ventilation, however, is not much different from the normal. Barr and Peters² obtained results closely approximating to our findings. The carbon dioxide percentage in the expired air is not conspicuously low, although it was found by comparison with a large number of normal individuals to be definitely below the average normal. This is particularly the case in subjects 1, 2, 3 and 5.

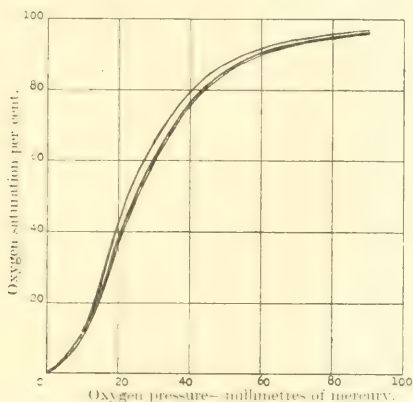


Fig. 4. Oxyhemoglobin curves calculated at carbon dioxide partial pressure of the alveolar air. Upper curve—Case 2. Middle curve—Cases 4 and 5. Lower curve—Case 3.

The production of carbon dioxide and the consumption of oxygen is under basal conditions not much different from normal. If there is any change it is towards a slight increase in the basal metabolic rate which is in accordance with the findings of Peabody, Wentworth and Barker¹⁸ in cases of "cardiac decompensation." Under conditions which were not basal, however, there was very little or no increase of metabolism permissible without conspicuous symptoms developing (Table VII and IX, Cases 1, 2 and 3). It would appear, therefore, that such cases as we have investigated were able to maintain a sufficient metabolism during basal or ordinary resting conditions, but any demand for a metabolism beyond a certain very circumscribed limit could not be met and serious and incapacitating symptoms

TABLE VII.
Pulmonary ventilation and basal metabolism.

Case	Date	Observations on ventilation rate	Respiratory rate per min.	Volume expired air per min. litres at S.T.P.	Volume expired air per resp. cycle at S.T.P.	Carbon dioxide	Oxygen taken up	Oxygen per min.	Surface area sq. met. 1.73 m.	Calories per sq. met.	Remarks
1	31.10.21	1	24	6.306	266	1.92	18.64	2.40	1.43	31.0	Normal rhythm
	1.11.21	2	28	8.020	258	2.12	18.42	2.52	"	41.0	"
	2.11.21	3	30	8.210	275	2.62	18.00	3.02	"	50.7	Exercise dyspnoea++
2	10.5.22	2	24	7.400	285	2.60	17.79	3.29	1.38	50.6	Exercise dyspnoea++
	27.6.22	3	20	6.820	340	3.30	18.05	3.05	1.37	43.0	Normal rhythm
	13.7.22	4	21	6.751	322	2.93	18.46	2.54	"	36.5	"
	21.8.22	5	16	5.400	341	2.73	17.67	3.40	"	38.8	"
	6.10.22	6	17	5.865	345	2.52	18.18	2.72	1.36	34.8	Basal conditions
	2.6.22	2	22	6.410	291	2.75	17.98	3.01	1.49	40.3	Arricular fibrillation
3	22.6.22	3	19	6.045	403	3.40	17.07	3.99	1.51	46.4	Normal rhythm
	7.7.22	5	14	6.692	478	3.01	17.70	3.30	1.53	42.6	"
	28.7.22	6	18	5.868	326	3.14	17.44	3.59	1.57	39.3	Arricular fibrillation
	28.8.22	7	16	5.920	370	3.27	17.49	3.49	1.56	39.3	Normal rhythm
	14.9.22	—	16	5.757	360	3.10	17.35	3.72	1.58	36.5	Normal basal conditions
	26.7.22	1	18	4.940	274	2.55	17.86	3.19	1.45	31.3	Normal rhythm
4	3.8.22	2	17	6.695	415	2.83	17.69	3.34	1.46	44.2	Exercise dyspnoea++
	11.8.22	3	18	5.440	302	2.85	17.55	3.52	1.45	39.0	Normal rhythm
	13.8.22	—	15	5.580	372	2.85	17.01	3.45	1.48	37.5	Basal conditions
	12.9.22	—	26	6.280	242	2.37	18.12	2.94	1.42	39.1	Arricular fibrillation
	16.9.22	—	34	8.806	259	1.94	18.82	2.18	1.40	40.2	Basal conditions

*Weights were all determined when the patients were free of obvious oedema.

would develop. These symptoms were not only respiratory in the form of dyspnoea, which was most obvious, but there was also fatigue, exhaustion and weakness. This would, therefore, indicate that the cause of the limitation of effort, and, therefore, the difficulty in increasing the metabolism was a general phenomenon, and was not confined to the pulmonary respiratory function as distinguished from the cellular respiratory function.

Physiological dead-space.

An explanation of the production of the lowered partial pressure of carbon dioxide in the alveolar air was not apparently to be obtained from the consideration of the pulmonary ventilation alone. The available evidence, however, was not considered complete without an investigation into the physiological dead-space. This was determined by the method of Douglas and Haldane.⁵ The results are set forth in Table VIII. It will be seen from these results that there is a distinct tendency, in the cases examined, towards a diminution in the dead-space. It was also found that, where symptoms would be most easily produced by exercise, so the dead-space was most reduced. This parallelism occurred in the following order: *Cases* 5, 4, 2, 1 and 3. But in *Case* 3 the conditions varied depending upon whether auricular fibrillation were present or not. If fibrillation were present, this case assumed a position analogous to *Case* 4, while if normal rhythm were present the capacity for effort and the dead space greatly increased. It will also be noted that the increase of the dead space runs in close parallelism to the increase of the carbon dioxide pressure of the alveolar air.

It may be considered probable, therefore, that the lowering of the alveolar carbon dioxide is accomplished by a diminution in the physiological dead-space and thus a closer approximation between the gaseous content of the expired and the alveolar air. This occurs not only in so far as the physiological dead-space for carbon dioxide is concerned, but also for oxygen. It is particularly evident in *Case* 5 where the oxygen and carbon dioxide dead-spaces are practically identical.

TABLE VIII.
Physiological dead-space.

Subject.	Cardiac rythm.	Dead-space <small>measured in cc.</small>	
		CO ₂	Oxygen.
1	Normal	154 cc.	
2	Normal	136	149
3	{ Auricular fibrillation Normal	121 } 172 }	164
4	Normal	114	142
5	Auricular fibrillation	104	103

The general circulation rate per minute.

In view of the respiratory and blood gas observations it seemed apparent that an adequate explanation of the dyspnoea and cyanosis, &c., in these cases of mitral stenosis was yet to be found. All the deviations from normal so far demonstrated appeared to be in the manner of compensatory phenomena and did not afford any elucidation or indication of the primary disturbance of function. On considering the character of the lesion and the circulatory pathology consequent upon it, it was obviously suggested that the primary disturbance of function was probably to be found in the circulation itself. This, therefore, necessitated an investigation of the general circulation rate.

Several means of determining this were considered and tried upon patients but with indifferent and inconsistent results. As a result a method already described from this laboratory¹⁵ was developed for employment in patients whose physical disabilities and lack of technical knowledge required some simple and easily repeated procedure. This method has been employed in the present observations.

In normal healthy individuals the findings vary according to age, sex, size and physical development of the individual. The volume of blood passing through the heart per minute and the volume expelled per beat, have been found to fall between certain broad limits in adults between the ages of 20 and 50.

TABLE IX.

Normal circulation rate and cardiac output per beat.

	Circulation rate per min.	Volume per beat.
Men	6.5 to 8 litres	90 to 120 cc.
Women	5.5 to 7 litres	80 to 100 cc.

In the cases of mitral stenosis investigated there was a great reduction, not only in the minute volume of the general circulation, but also in the output per beat. The various observations in these cases are set forth in Table X. In *Case 5* severe respiratory symptoms were so readily induced that it was found impossible for the patient to carry out the procedure for estimating the venous carbon dioxide pressure. The results of the few attempts in this case have therefore been omitted. The other cases, after several trials, soon became quite adept in the procedure and carried it out with expedition and accuracy.

The estimation of the venous carbon dioxide pressure was made by beginning with a low percentage of this gas in the bag and working upwards. After several stationary estimations were obtained carbon dioxide was

added to about 7 per cent. and the air rebreathed until a similar number of stationary readings were obtained from above downwards. These two sets of stationary readings invariably coincided very accurately. In Fig. 5 is shown a typical series of estimations plotted in sequence.

In these cases of mitral stenosis there is a conspicuous reduction in the general circulation rate. This is clearly demonstrated in *Cases* 1, 2 and 4. In all of these cases there was pronounced stenosis as demonstrated by the cardiac examination. The lesion appeared to be most advanced in *Cases* 1 and 4. It will be observed that although the general circulation rate in these cases was not much different from that in *Case* 2, there was, however,

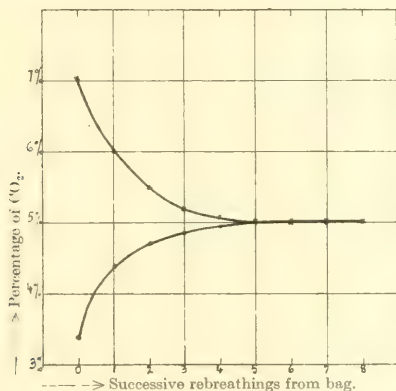


Fig. 5. Approximation of the venous CO₂ percentages from lower and higher concentration.

a considerably faster cardiac rate, the complement of which is evident in the definite decrease in the output per beat. It must also be noted, as shown in Table VI, that the height and weight (surface area) of *Case* 2 is somewhat less than in *Cases* 1 and 4.

The response to exercise in three of the *Cases* (1, 2 and 4) is also quite clear. The outstanding feature was the pronounced increase in the severity of the symptoms. Although there is a comparatively moderate increase in the general circulation rate there is a very conspicuous increase in the cardiac rate and a slight but consistent decrease in the cardiac output per beat, which, if the exercise had been pushed to a greater degree, would most probably have been more conspicuous.

In *Case* 3 we were fortunate in being able to make observations during both normal rhythm and periods of auricular fibrillation. The degree of mitral stenosis was not conspicuous as compared with *Cases* 1, 2 and 4, but it

TABLE N.

General circulation rate, random output per beat, etc., in cases of mitral stenosis

Case.	No. of Observations.	Date.	Arterial CO ₂ pressure.	Venous CO ₂ pressure.	Arterial CO ₂ vol. %.	Venous CO ₂ vol. %.	Difference.	CO exp. per min. cc.	Blood flow per min. litres.	Pulse rate per min.	Vol. per beat	Remarks.
1	1	31.10.21	31.9	39.6	46.5	50.7	4.2	123	2.93	90	32	Regular rhythm.
	3	1.11.22	32.6	40.4	46.9	51.2	4.3	216	5.00	158	32	Walking exercise - severe dyspnoea
	2	2.11.22	32.4	40.9	46.8	51.4	4.6	170	3.69	110	33	
2	1	9.5.22	28.8	37.9	44.7	49.9	5.2	147	2.82			Normal rhythm.
	2	10.5.22	28.6	38.2	44.5	50.0	5.5	190	3.45	80	43	Mild exercise - dyspnoea.
	3	27.6.22	25.2	33.0	42.2	47.2	5.0	155	3.10	64	48	Normal rhythm.
	4	13.7.22	26.0	34.9	42.8	48.2	5.4	149	2.76	60	46	" "
	5	21.8.22	26.0	34.4	42.8	48.0	5.2	149	2.86	62	46	" "
3	1	26.5.22	32.9	41.0	47.1	51.5	4.4	168	3.82	84	45	Auricular fibrillation.
	2	2.6.22	34.3	43.4	47.9	52.7	4.8	177	3.98	130	28	" "
	3	22.6.22	39.1	46.9	50.5	54.3	3.8	204	5.35	54	99	Normal rhythm.
	4	27.6.22	39.2	48.2	50.6	54.8	4.2	196	4.66	62	75	" "
	5	7.7.22	37.5	45.7	49.6	53.7	4.1	189	4.61	72	64	" "
	6	8.7.22	35.2	44.2	48.4	53.0	4.6	182	3.95	80	49	Auricular fibrillation
	7	28.8.22	38.8	48.8	50.4	55.0	4.7	194	4.21	67	63	Normal rhythm.
4	1	26.7.22	32.4	39.3	46.8	50.6	3.8	125	3.20	94	35	Normal rhythm.
	2	3.8.22	32.8	39.7	47.0	50.8	3.8	188	4.94	150	33	Walking exercise - - very dyspnoea.
	3	11.8.22	31.6	39.0	46.3	50.4	4.1	150	3.65	92	39	Normal rhythm

was still quite definite. It will be noted that in observations 1 and 6 the general circulation rate only differed by 130 cc., while the pulse rates were almost equal but with an inverse output per beat—the slower the rate the greater the output per beat and per minute. This is further emphasized in observation 2, where the cardiac rate increased to 130 and the output fell to 28 cc. per beat. A logical explanation of this is to be found in the character of the tachycardia and the presence of the mitral stenosis. When the rhythm returned to normal with a bradycardia, the general circulation rate greatly increased with a coincident increase in the output per beat. This circulatory improvement was further emphasized by the great activity and feeling of well-being of the patient after many weeks of invalidism. But with the gradual increase of the cardiac rate the general circulation showed a comparatively moderate slowing, and the output per beat proportionately decreased. The pronounced increase in the metabolic rate in observation 3 may have partly accounted for the increase in the general circulation rate. A comparison of observations 5 and 7 demonstrates how closely the conditions are reproduced, as has already been mentioned, as occurring during similar periods of auricular fibrillation.

Discussion.

In investigating these cases of mitral stenosis we have been trying to explain, if possible, the meaning of the chief symptoms—dyspnea, palpitation, tachycardia, exhaustion, weakness, cyanosis, etc., which are so typical of this disease but also so diverse in their manifestations. It is difficult, if not well-nigh impossible, to find cases in exactly the same degree of pathological development. Therefore due allowance must be made for the varying degrees of the severity of the lesions. Some of the cases developed symptoms on much less provocation than did others. This was to be expected. As has already been mentioned, many of the deviations from normal in the respiratory and blood gas analyses appeared to be in the manner of compensatory phenomena. But for what disturbance of physiological function they were compensating was not clear until an investigation of the general circulation rate was completed. The most conspicuous and constant fact observed in this regard was the pronounced decrease in the output per beat of the heart. Instead of the volume of blood per beat being 80-100 cc., it was found to be but 35-45 cc. An explanation of this diminished output was, possibly, to be found in the character of the cardiac lesion.* As the orifice of the mitral valve becomes smaller and smaller, the amount of blood which could pass from the auricle to the ventricle would probably become proportionately less in a given period of diastole. In regular cardiac rhythm the

* It has been appreciated by us that there are at least two factors, namely, the valvular lesion and failure of the cardiac muscle—operative in producing the cardiac inefficiency observed in such cases as here reported. As yet we have been unable to determine the relative importance of these two factors.

auricular systole would gradually assume a greater proportionate rôle in introducing blood into the ventricle*. But as the resistance became greater even this factor would be expected to suffer certain embarrassment. It is suggested that there may be a definite relationship between the degree of stenosis and the diminution in the cardiac output per beat.

The impairment of the cardiac output per beat could be partially compensated for by an increase of the cardiac rate, but this, it has been found, has not been proportionately the case. Therefore there has been a consistent diminution in the minute volume of the general circulation rate. Even at rest it is necessary for the cardio-vascular system to maintain a more or less efficient circulation rate in order to maintain the needs of metabolism. If this were not the case there would be a gradual cessation of certain of the functions even at rest. That an increased cardiac rate was necessary to maintain this level is demonstrated in *Cases 1 and 4*. It is further evident that these cases even under basal conditions are almost at their limit of metabolic activity. Any notable increase of metabolism, beyond that of basal conditions, demanded by slight exertion produced symptoms out of all proportion to the work done. Furthermore this was only accomplished by a conspicuous increase in the cardiac rate and by what is very significant, namely, a slight but constant decline in the volume output per beat.

Under such conditions it would not be considered probable that all the tissues would be as freely supplied with blood as under normal conditions. The increased cardiac and respiratory efforts would require a greater supply than normally. Therefore it would be expected that certain tissues would have their circulation relatively reduced during periods of rest. The reduced oxygen saturation and increased carbon dioxide content of the venous blood from the arms and hands would indicate that the skeletal structures, during periods of rest, were being more or less automatically deprived of their normal quantity of arterial blood. In other words the skeletal structures during periods of rest were standing the brunt of the lowered circulation rate in these cases. This would indicate a relative circulatory stasis.

Those organs most essential for carrying on life would, of necessity, obtain an adequate amount of blood. The skeletal structures which at rest are but little used would naturally require but a scant supply. In this way a certain conservation could be effected. In accordance with the degree of slowing of the general circulation rate, so these vitally less essential tissues would obtain a diminished supply of blood. The very slow circulation through the extremities, such as the hands, feet, ears, lips and nose, would be equivalent to a relative stasis. A natural result of such a condition would be a rapid lowering of the oxygen saturation and an increase of the carbon dioxide content of the capillary blood which would be reflected in the

* This rôle of the auricle would practically disappear in auricular fibrillation.

condition in the venous blood draining the part. In this way the occurrence of a purplish cyanosis in the peripheral areas would be accounted for. The occurrence of vascular stasis with all its consequent disturbances of cellular reaction with acidosis and swelling, as demonstrated in a former paper, will be readily understood. We consider this probably an important factor in the production of cardiac oedema. The mere occurrence of slowed circulation with mechanical squeezing out of fluid into the surrounding extravascular spaces does seem to adequately explain the production of oedema in all cardiac cases. The evidence indicating a definite change in the blood coming from the capillaries under such circumstances appears to be complete.⁶ This would point to the occurrence of a relative gaseous acidosis in the cells which would not be equal in all cases. Those with the severest cardiac inefficiency and proportionate slowing of the general circulation rate would be most likely to show the peripheral signs most completely.

We would suggest that the cause of the dyspnoea in these cases is due to an analogous course of events. The respiratory centre would suffer along with other structures from the effects of a relatively slow circulation through it. As a consequence there would be a persistent tendency to develop a gaseous cellular acidosis. This the respiratory centre would attempt to overcome by increasing the pulmonary ventilation to reduce the carbon dioxide partial pressure of the mixed alveolar air and as a result reduce the carbon dioxide content of the arterial blood. This would produce a gaseous alkalosis of the arterial blood which, however, would be defeated in its beneficial influence if the bicarbonate reserve of the arterial blood were lowered. There is, however, no evidence of this lowering taking place. As the arterial blood reaches the tissues in a more or less alkaline condition, due to a depreciation of the carbon dioxide content, it would more readily take up carbon dioxide from the tissues which are suffering from an impending gaseous acidosis.

The effect of a slight gaseous acidosis of the respiratory centre would be enhanced by the threatened development of a cellular oxygen want. An ultimate effect of the slowing of the circulation through the respiratory centre is to be found in the development of orthopnoea and in certain cases of (Cheyne-Stokes) periodic breathing.

An accentuation of all the symptoms by exercise is to be found in the milder cases. Due regard, however, must be allowed for the increased metabolism when comparing the detailed findings with those of the resting condition. When such cases of mitral stenosis undertake physical exertion the increase of the general circulation rate is accomplished, as is usual in normal cases, by an increase of the cardiac rate. As the blood supply to the skeletal tissues is obviously much below normal at rest the abnormal demand can only be met if the exercise be within certain limits. Such limits will depend upon the degree of the pathological lesion present. It is, in the main, the deficient supply of saturated oxyhæmoglobin which

limits the capacity for physical exertion. If the exercise be pushed beyond a certain limit a general cyanosis develops which is of a deep purple hue, indicating the presence of high carbon dioxide tension with a lowered oxygen pressure in the blood of the capillaries. This has been demonstrated by direct observation of the venous blood which shows under these circumstances a greatly decreased oxygen saturation of the oxyhaemoglobin and high carbon dioxide tension, although the carbon dioxide combining power is acutely diminished. Direct examination of the gaseous content of the arterial blood has not been possible in these circumstances. But there is presumptive evidence that the arterial blood may not be completely oxygenated, as the inhalation of oxygen gives a certain amount of relief and the degree of cyanosis is less on the same amount of exercise.

The explanation of the gradual and progressive aggravation of the symptoms in these cases during moderately active life is not quite clear. There is no evidence that the stenosis changes in degree, thereby offering an increasing impediment to the general circulation. It seems more probable that the explanation must be sought in the fact that through a gradual accumulative but slight deficiency of blood supply to the cardiac and other tissues their efficiency slowly deteriorates with the development of a vicious circle in the cardio-vascular system. With prolonged rest the condition gradually returns to a state of more or less efficient equilibrium which in some cases may be more pronounced than others, depending upon the chronicity and aggravation of the symptoms, the degree of stenosis and the permanent damage to the myocardium and others tissues.

CONCLUSIONS.

1. The general symptoms, dyspnoea, cyanosis, weakness, fatigue and exhaustion, in cases of mitral stenosis are primarily due to a reduction of the general circulation rate. This is evident at rest but is more conspicuous on exercise, particularly when the work accomplished is compared with the symptoms produced.

2. There is no evidence that in the absence of pulmonary complications there is any deficiency in the oxygen saturation of the arterial blood.

3. The carbon dioxide content of the arterial blood is diminished, but the carbon dioxide combining power of the arterial blood remains normal while that of the venous blood is definitely diminished. The pH of the arterial blood inclines towards an increase of alkalinity while the venous blood is relatively more acid.

4. These deviations from normal are compensatory phenomena necessary to maintain the cellular equilibrium of those parts insufficiently supplied with blood.

5. In order that this compensation may be maintained, the alveolar carbon dioxide partial pressure is diminished and the oxygen partial pressure is increased.

6. The variations in the oxy-hæmoglobin dissociation curves are not beyond the limits of normal, considering the carbon dioxide partial pressure of the alveolar air. Therefore there is no evidence that the tissues cannot acquire oxygen as readily as under normal conditions in so far as the dissociation of oxy-hæmoglobin is concerned.

7. The slowing of the general circulation rate indicates that certain tissues would not obtain a sufficiency of oxy-hæmoglobin to maintain their functional efficiency under conditions of work. Further, if this slowing of the circulation proceeded beyond certain limits, the necessary requirements for resting conditions could not be maintained, and signs of circulatory failure would become evident.

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THE EFFECT OF VAGAL STIMULATION ON INTRA-AURICULAR BLOCK PRODUCED BY PRESSURE OR COOLING.*

By T. LEWIS and A. N. DRURY.

(*University College Hospital Medical School.*)

Historical.

IN 1883, Gaskell¹ reported his experiments upon the tortoise auricle. He slit up the auricle so as almost to divide it into two parts, the one attached to the sinus, the other to the ventricle, these two parts being left united at one point by a narrow bridge of muscle tissue. If the bridge is rendered sufficiently narrow, it becomes incapable of conveying each impulse from the spontaneously beating basal portions of the preparation; the bridge constitutes a point of block. Gaskell tested the effects of vagal stimulation upon this block. He states that right and left vagus possess the power of removing a partial block. He writes: "This improvement of conduction power is, like the improvement in the force of the contractions or the after-acceleration, spread over a long period of time, so that in most cases stimulation of the nerve removes the partial block altogether." Again, he states, "every second contraction passes before the stimulation, then during and after the nerve stimulation every contraction passes, and then again in a very short time only every second contraction is able to pass." Still later he states, "I possess but few curves which show unmistakably any diminution of conduction power in consequence of nerve stimulation. Still, as Figs. 12 and 13, Pl. IV., show, such an increase in the extent of the block does undoubtedly sometimes occur."

To be understood, these statements require further examination. The decrease of the original block *during* vagal stimulation, which Gaskell saw, was accompanied by a lowering of the rate of sinus beating and resulted from this lowered rate of beating, the longer rests and consequent greater recovery of the tissue bridge between the beats. Where there was no decrease, or no

* Observations carried out on behalf of the Medical Research Council. We desire to acknowledge the valuable assistance which we have received from Dr. A. M. Wedd, of Pittsburgh, and Dr. C. C. Ilescu, of Bukarest, in these experiments.

A preliminary account of these experiments appeared in the *Proc. Physiol. Soc.*, February 18th, 1922.

appreciable decrease, in the rate of sinus beating under vagal stimulation, the block was increased, as his curves clearly show. In these descriptions of Gaskell's experiments there is no evidence to show that during vagal stimulation the tissue of the bridge is capable of conducting impulses more effectively than before the nerve stimulation was applied, the improvement of conduction which he here describes is not the direct outcome of vagal stimulation, but is secondary to a change of rate. Two figures which he uses as illustrations show no change of sinus rate, and in both these nerve stimulation produces a greatly enhanced block. It is here to be observed, however, that in his subsequent remarks, Gaskell refers to instances in which, though the rate was not reduced, the block became decreased. Since these instances are not illustrated, it does not seem to us entirely clear that the block was relieved actually during the stimulation, though this is the actual statement in the text. It seems to us that Gaskell is probably here describing the effects immediately following nerve stimulation.

Such effects are perfectly clearly illustrated and described in other places. The usual effect of vagal stimulation, when a partial block has been established, is a lowered rate of sinus beating and the passage of the bridge by each impulse *during* stimulation; immediately stimulation is withdrawn there is a rebound from inhibition, and the beats of the sinus, now accelerated, pass the bridge regularly and for considerable periods of time.

From Gaskell's description of the tortoise auricle therefore, it is quite clear that vagal stimulation may decrease the conduction power of the bridge; it is equally clear that the original block usually becomes reduced as an immediate *after effect* of stimulation; it is not quite clear if, in exceptional cases, he saw an actual increase in the bridge's capacity to conduct *during* vagal stimulation.

Gaskell's observations are summed up in his sentence: "Although the initial effect of the vagus is to depress some function, its final and most enduring power is to exalt, intensify and repair that function."

In Engelmann's experiments³ a clamp was applied to the auricle, and the interval between the contractions of the proximal and distal segments was measured. These experiments afford little information from our present standpoint, as little or no change of interval was observed during stimulation, and for the most part vagal stimulation produced much slowing of the heart.

Garrey¹ used the turtle's heart. He produced intra-auricular block by applying a clamp between the right and left auricle and obtained results with vagal stimulation, which he describes as invariable. When he stimulated the left nerve and obtained no alteration of basal rate, the block was always increased; when he stimulated the right nerve and obtained little reduction of rate, a similar effect was observed: when on stimulating the right nerve, the basal rate was much reduced, the degree of block diminished. Garrey's experiments, and his discussion of them, particularly emphasise the double influence of the vagus, its direct and depressing effect

on the one hand, its effect of relieving block indirectly by reducing the rate at which impulses impinge on the bridge, on the other.

To sum up, so far as the cold-blooded auricle is concerned, there is definite and unanimous evidence that vagal stimulation will further decrease the power of conduction when this is originally lowered by clamping, or by other injury. There is insufficient evidence that the reverse effect occurs, though certain of Gaskell's statements may be read to imply that this reversed action is sometimes seen.

So far as the mammalian auricle is concerned, we are aware of few observations. It has been shown by Lewis, Meakins, and White,¹¹ and more recently and conclusively by Lewis, Drury, and Bulger,⁸ that the rate of conduction in the uninjured dog's auricle, beating at normal rates, is uninfluenced by vagal stimulation (right or left). But it was shown by the same workers⁸ that when the rate of conduction is lowered as a consequence of raised rate of beating, that vagal stimulation in these circumstances invariably improves conduction, increasing the rate until it reaches its original value. Similar observations have been made on the intra-auricular block produced by strophanthin poisoning.⁹ Both these effects have been attributed to a reduction of the refractory period of the auricle under vagal stimulation. A similar effect of vagal stimulation is observed when conduction in the auricle is retarded as a consequence of quinidine poisoning though the nature of this reaction is less clear.¹⁰

In view of these observations we decided to test changes in conduction in the auricle under vagal stimulation more extensively, and first describe our observations upon intra-auricular block produced by compression. These were intended primarily to test the question as to whether there is an essential difference between the action of the vagus in intra-auricular block produced by compression or similar damage, in the cold and warm-blooded heart.

Observations on block produced by compression.

The auricular appendages are parts of the auricle, which are peculiarly suited to observations such as are to be described, for they form natural projections which may be compressed at their bases without unduly interfering with the circulation. The experiments to be described were performed upon the right appendix almost exclusively.* Desiring to interfere but slightly with the transit of the naturally conducted impulse from the body of the auricle along the line of the auricular appendix to its tip, we devised, and at first used, a pneumatic clamp. The jaws of this clamp were rigid, but one was covered by a flexible rubber membrane which could be ballooned against its fellow at varying pressures. The pressures employed

* On two occasions the chief observation of this section has been successfully carried out on the left appendix.

varied up to and somewhat beyond 300 mm. Hg: but we were disappointed to find that such grades of compression failed to produce the desired effect, namely, an impaired conduction through the tissues of the bridge. It became obvious that the degree of compression required to produce block of different degrees could not be attained conveniently by means of pneumatic compression: a solid metal clamp was therefore built, which would submit the muscle to much higher pressures. The jaws of this clamp were 1 centimetre wide, flat, and smooth, one jaw being moved to meet its fellow by a very fine screw having 60 threads to the inch.

The method of experiment is as follows:—Dogs of about 10 kilogrammes weight are employed and these are fully anaesthetised with morphia, paraldehyde and ether. The heart is exposed, the tip of the right appendix secured and passed through the jaws of the clamp, until the latter rests at the base of the appendix. The tip of the appendix is then fastened without material tension to a convenient part of the chest wall, and the clamp secured to an adjustable stand. Two pairs of non polarisable contacts are now placed in the line of the auricular appendix, one pair lying proximal and the other distal to the clamp; gaps of about a centimetre being allowed between the edges of the clamp and the nearest contacts, to avoid disturbance of the contacts on tightening the clamp. Each pair of non-polarisable contacts is connected to one string of the recording galvanometer. A pair of stimulating electrodes is placed on the body of the right auricle, and in line with the two pairs of recording contacts, and into these rhythmic induction shocks are sent, at a rate slightly surpassing the rate of the natural heart beat after section of the two vagi. To these rhythmic shocks, which are maintained throughout the experiment, the auricle responds, and with each response the excitation wave passes to the proximal contacts, across the area involved by the clamp and to the distal or appendicular contacts; the arrival of the wave at the two pairs of contacts is thus recorded, and the corresponding transmission intervals are subsequently measured.

By graduating the clamp pressure it is easy to obtain various grades of block between the body of the auricle and the appendix. The first change observed on tightening the clamp is a widening of the transmission interval: this widening increases until the auricular appendix occasionally fails to respond: with more severe pressure this failure to respond becomes more frequent, 2:1 block becomes established, and finally, with heavy pressure, no beats are transmitted.

At any of these stages, the effect of vagal stimulation upon the block so induced may be tested. It is to be observed, however, that if pressure is applied and a certain grade of block is obtained, maintenance of this same pressure for unduly long periods of time is accompanied by an increase in the grade of block; the pressure used is much more than is sufficient to bring the blood supply to the appendix to an end, and the muscle will not continue for many minutes to beat in these circumstances. It is necessary, therefore, by preliminary tests, to gain an idea of the pressure needed to

produce a desired grade of block, and to apply this pressure without undue delay: otherwise a sufficient period of uniform block will not be obtained for the purposes of the test. A period of time sufficient for the test of vagal stimulation and subsequent recovery from this test is required. The latter is not always but is usually obtainable. A period sufficient for two complete tests is not usually attainable: it is best to withdraw the pressure as soon as the first test is complete, and to reapply it subsequently in further tests, since severe initial pressure is usually required: its early withdrawal in observations in which complete block is produced by clamping is especially desirable. For, if severe pressure is maintained unduly, recovery of conduction on removing the clamp is very slow, occupying half an hour or more. In the case of lesser grades of block, recovery on removing the clamp usually occurs within a few seconds or at the most minutes.

When the vagal stimulation affects blocks so produced it does so in an almost constant manner, it reduces the block: and this statement applies to each degree of block. The reduction of the block usually occurs promptly, and is maintained throughout stimulation. The block reappears shortly after vagal stimulation ceases.

Exceptionally vagal stimulation fails to affect the block: this happens in two circumstances. Firstly, if the vagus is inactive or is inadequately stimulated. Whether the vagus has or has not acted on the heart is known from an examination of the records: for although these records are essentially auricular records, a small and clear ventricular representation is also seen in them. This disappears under vagal stimulation, as does the ventricular beat in a simultaneous ventricular myogram, because A-V block becomes established. It is to be remembered that the auricular rate is being maintained at 160-210 throughout the observation, and that in this circumstance both right and left vagus yield high grades of A-V block. We use such strengths of vagal stimulation as will bring the ventricle to a standstill or will induce a high grade of partial A-V block, and this A-V block forms a safe control of the general influence which the vagal stimulation has exerted in each observation. Secondly, the vagal stimulation may fail to affect the block if the pressure exerted by the clamp has been too great or has been too long maintained. Such exceptions are exclusively instances of block originally complete in its degree, and in all such recovery from block on releasing the clamp has been long delayed. In such experiments failure to obtain the usual vagal effect may be due to death of the muscle fibres, though this is rarely the case, since ultimate recovery of conduction is almost invariable: it is more probably due to damage of the nerve fibres beneath the clamp. In several instances, after releasing the clamp, a complete block has been maintained for periods of many minutes and even of 40 minutes, yet at any time during this period the block could at once be broken down temporarily to a 1:1 response by stimulating the vagus (Dog NY, record No. 16). In a solitary instance (Dog NZ, record No. 3) a slightly prolonged interval (A-A was not reduced by effective vagal

stimulation; in a solitary instance (Dog NX, record No. 3) a prolonged interval was slightly increased by vagal stimulation. For these two minor exceptions we have no explanation to offer.

Reduction in the degree of block is produced by stimulating either the right and left vagus, and in our experiments the two nerves have seemed equally effective in this respect.

Complete abolition of the block is not usually seen, though the block is almost abolished. Thus, although complete block is always reduced to a condition in which there is invariable response, yet the short original transmission interval is not generally reached. It may be reached, and is often almost reached, but even at the height of the reaction, the intervals usually remain a little lengthened. Failure to reduce the block entirely is evidently due, in large measure at all events, to damage produced by the clamp. After clamping and releasing the muscle, the original intervals are not usually entirely restored; if time is allowed, recovery occurs but is rarely quite complete. It would appear that conduction, depressed by clamping, is restored or greatly improved by vagal stimulation; when under vagal stimulation a slight defect still remains, it may be ascribed in part at least, to permanent damage of the tissue, perhaps through interference with its blood supply.

The after-effects of vagal stimulation as opposed to the effects witnessed during stimulation, are more difficult to study. Usually the degree of block preceding vagal stimulation reappears; but the after-effects are not infrequently complicated by increase in the grade of block consequent on the clamp pressure being maintained; for the effect of the clamp is the establishment of a certain grade of block, which after a time tends to increase if pressure is continued.

These observations are illustrated by records and by Table I. In Fig. 1 the top curve (*V.M.*) is a ventricular myogram, in which the beats of the ventricle (*v*) are clearly shown. The centre curve (*APP*) is an electrogram from the appendix distal to the clamp; the lowest curve is an electrogram from the body of the auricle, proximal to the clamp. Throughout the record the clamp was on; the body of the auricle is beating in response to rhythmic shocks, entering it at a rate of 167 per minute, as shown by the sharp deflections in the lowest curve; the ventricle is responding to the auricle at the same rate, its movements being recorded by the myograph and by the small deflections *v* in the lowest curve. On the other hand, the appendix is not responding: complete block between it and the body of the auricle exists. Shortly after vagal stimulation begins the ventricle stops beating, and almost immediately the appendix responds for the first time (beat 5): the appendix fails to respond to the next impulse (beat 6), but responds regularly to impulses 7, 8, 9, 10, etc.. Thus, while the vagal stimulation produces a profound degree of block at the *A-V* junction, it quickly relieves the block previously produced at the base of the auricular appendix by the clamp.

TABLE I.
Influence of equal stimulation upon intra-auricular block produced by compression.

Dog.	Record No.	Controlled auric. rate.	Before stimulation.	Conduction.	During stimulation.	Vagus	Cool at	Simultaneous effect on A-V conduction.	Remarks.
NV	2	187	1:1 (1-1* 0.6589)	1:1 (1-1 0.6503)	right	5.0 cm.	9:1, 4:1, 3:1	Clamp reapplied.	
	3	187	3:1	1:1 (1-1 0.6516)	right	5.0 cm.	3:1	Clamp reapplied.	
	4	187	3:1	1:1 (1-1 0.6570)	right	5.0 cm.	3:1, 2:1, 3:1, 3:1	Clamp reapplied.	
	6	185	4:1	1:1 (1-1 0.6705)	right	5.0 cm.	3:1	Clamp reapplied.	
	7	185	2:1	1:1 (1-1 0.6754)	left	5.0 cm.	5:1, 4:1	7 mms. after releasing clamp.	
	8	187	2:1	1:1 (1-1 0.6660)	left	5.0 cm.	4:1, 2:1, 2:1	9 mms. after releasing clamp.	
	3	200	Complete block	1:1 (1-1 0.6604)	right	5.0 cm.	Standstill of ventricle	Clamp reapplied.	
	3	200	"	1:1 (1-1 0.6449)	right	5.0 cm.	"	3 mms. after releasing clamp.	
NW	4	200	" (1-1 0.6622)	1:1 (1-1 0.6534)	right	5.0 cm.	"	Clamp reapplied.	
	5	200	2:1 (1-1 0.6600)	1:1 (1-1 0.6600)	right	6.0 cm.	"	Clamp reapplied.	
	6	200	2:1 (1-1 0.6181)	1:1 (1-1 0.6559)	left	5.5 cm.	4:1, 4:1, 6:1	Clamp reapplied.	
	2	180	1:1 (1-1 0.6317)	1:1 (1-1 0.6469)	right	5.0 cm.	3:1, 2:1, 2:1, 2:1	Before clamping. Clamp applied.	
	3	183	1:1 (1-1 0.6400)	"	"	"	"	2 mms. after clamp released.	
	4	180	1:1 (1-1 0.6330)	"	"	"	"	Clamp reapplied.	
	5 & 6	187	Complete block	Complete block	right	5.0 cm.	2:1	Clamp reapplied.	
	8	206	Occ. dropped beat	1:1 (1-1 0.6609)	right	4.5 cm.	2:1	11 mms. after clamp released.	
NX	9	206	1:1 (1-1 0.6362)	"	"	"	"	Clamp reapplied.	
	10	210	2:1 (1-1 0.6150)	2:1 (1-1 0.6030)	right	4.0 cm.	5:1, 3:1	Clamp reapplied.	
	11	208	Complete block	Complete block	right	4.0 cm.	4:1, 4:1, 3:1	4 mms. after clamp released.	
	12	208	"	2:1	left	4.0 cm.	5:1, 4:1, 3:1, 3:1	Clamp reapplied.	
	13	205	"	Complete block	left	4.0 cm.	5:1, 6:1, 4:1, 3:1	Clamp reapplied.	
	14	200	"	1:1 (1-1 0.6544)	left	4.0 cm.	5:1	Clamp reapplied.	
	15	205	"	2:1, later 1:1	left	4.0 cm.	6:1	Clamp reapplied.	
	16	160	V. occ. responses	1:1 (1-1 0.6373)	left	4.0 cm.	5:1, 7:1	10 mms. after clamp released.	

* A-V Conduction interval between auricular contacts.

TABLE I.—*continued.*

Dog.	Record No.	Core- tested aortic rate	Before stimulation.	Conduction	Diastolic stimulation	Vagus.	Cord at	Simultaneous effect on A-V conduction	Remarks
NX— <i>cat.</i>	17	158	Complete block	1:1 (1:1—0.0397)	right	4.0 cm.	6:1, 5:1	11 mins. after clamp released.	
	18	158	6:1	1:1 (1:1—0.0406)	right	4.0 cm.	6:1	16 mins. after clamp released.	
	19	177	1:1 (1:1—0.0400)	—	—	—	—	21 mins. after clamp released.	
	20	165	Complete block	1:1 (1:1—0.0836)	left	3.0 cm.	6:1, 5:1	Clamp resupplied. 29 mins. after clamp released.	
	21	163	1:1 (1:1—0.0425)	—	—	—	—	Clamp resupplied.	
	22	167	Complete block	2:1, later 1:1 (1:1—0.0742)	right	—	6:1, 5:1	Clamp resupplied.	
NY	23	167	1:1 (1:1—0.0411)	—	—	—	—	12 mins. after clamp released.	
	1	172	1:1 (1:1—0.0403)	—	—	—	—	Before clamping. Clamp applied. 5 mins. after releasing clamps.	
	2	172	Complete block	1:1 (1:1—0.0558)	right	4.0 cm.	Standstill of ventricle	Clamp resupplied.	
	3	172	1:1 (1:1—0.0318)	—	—	—	—	Clamp resupplied.	
	3a	174	Complete block	1:1 (1:1—0.0742)	left	5.5 cm.	Standstill of ventricle	Clamp resupplied.	
	4	172	2:1 (1:1—0.0798)	1:1 (1:1—0.0733)	right	3.5 cm.	—	Clamp resupplied. 2 mins. after releasing clamps.	
	5	174	1:1 (1:1—0.0412)	—	—	—	—	Clamp resupplied.	
	6	172	Complete block	1:1 (1:1—0.0568)	left	5.5 cm.	4:1	Clamp resupplied. 7 mins. after releasing clamps.	
	7	173	1:1 (1:1—0.0404)	—	—	—	—	Clamp resupplied. Res- clamping.	
	11	176	1:1 (1:1—0.0612)	—	—	—	—	Clamp resupplied. Res- clamping.	
	12	175	Complete block	1:1 (1:1—0.0399)	right	4.5 cm.	Standstill of ventricle	About 3 mins. after release of clamp.	
18 & 19	13	175	" "	1:1 (1:1—0.0625)	left	4.5 cm.	" "	5 mins. after release of clamp.	
	16	175	" "	1:1 (1:1—0.0260)	right	5.5 cm.	4:1, 4:1, 4:1, 2:1	40 mins. after release of clamp. repeated several times.	
	17	175	" "	1:1 (1:1—0.0444)	right	5.5 cm.	Standstill of ventricle	—	
	18	180	1:1 (1:1—0.0659)	—	—	—	—	58 mins. after re- leasing clamp.	
	19	180	1:1 (1:1—0.0485)	—	—	—	—	—	

NZ	20	189	Complete block	1:1 (A, A=0.0129)	right	4.5 cm.	"	"	10 mins. after releasing clamp. Same effect repeated 5 times during next 10 mins. Effect abolished by atropine.
OB	2	175	1:1 (A, A=0.0321)	1:1 (A, A=0.0112)	right	6.0 cm.	Standstill of ventricle	Before clamping. Clamp applied. 4 mins. after releasing clamp.	
	3	175	1:1 (A, A=0.0107)		—				
	4	175	1:1 (A, A=0.0375)		—				
	5	177	1:1 (A, A=0.0574)	1:1 (A, A=0.0543)	right	6.0 cm.	High grade of block	Clamp reapplied. 4 mins. after releasing clamp.	
	6	179	1:1 (A, A=0.0479)		—				
	7 & 9	179	2:1	1:1	right	6.0 cm.	High grade of block	Clamp reapplied.	
	16	180	1:1 (A, A=0.0788)*	1:1 (A, A=0.0718)	right	5.0 cm.	2:1, 8:1	Clamp reapplied. 4 mins. after releasing clamp.	
	17	182	1:1 (A, A=0.0536)		—				
	18	185	1:1 (A, A=0.0705)	1:1 (A, A=0.0647)	right	5.0 cm.	1:1, 3:1, 5:1	Clamp reapplied.	
	1	172	1:1 (A, A=0.0316)	—	—			Before applying clamp.	
	2	172	1:1 (A, A=0.0588)	1:1 (A, A=0.0512)	right	4.5 cm.	2:1, 2:1, 2:1	Clamp applied. 27 mins. after clamp released.	
	3	171	1:1 (A, A=0.0370)		—				
	4	171	Very occ. response	1:1 (A, A=0.0535)	right	4.5 cm.	2:1, 2:1, 2:1	Clamp reapplied. 3 mins. after clamp released.	
	5	172	1:1 (A, A=0.0408)		—				
	6	172	1:1 (A, A=0.0531)	1:1 (A, A=0.0370)	left	4.5 cm.	2:1, 2:1, 2:1	Clamp reapplied. 6 mins. after clamp released.	
	7	171	1:1 (A, A=0.0369)		—				
		171	Complete	1:1	right	4.5 cm.	Heart block	Clamp reapplied and released; oxidation repeated and same effect obtained. <i>Uterine contraction after atropine; other cardiac arrhythmias undisturbed.</i>	
		172	"	Complete	right	4.5 cm.	No block	Same repeated with right and left vagus with minor results. 24 mins. after clamp released.	
	10	172	1:1 (A, A=0.0793)	1:1 (A, A=0.0471)	right	4.5 cm.	No block		
	12	172	Very occ. response	Very occ. response	right	4.5 cm.	No block	Clamp reapplied	

* This interval (and those which follow) is not comparable with those which precede it in the same column; the contractions having been missed.

TABLE II.

Influence of vagal stimulation upon intra-auricular block produced by cooling.

Dog.	Record No.	Controlled auric rate.	Temperature.	Conduction		Effect on A-V conduction.	Vagus.
				Before stimulation.	During stimulation.		
OM	26	175	36°C	1:1 (1:1, 1-0.0585)	1:1 (1:1, 1-0.0576)	Standstill of ventricle	Right
	23	178	30°C	1:1 (1:1, 1-0.0625)	1:1 (1:1, 1-0.0619)	"	"
	24	176	25°C	1:1 (1:1, 1-0.0700)	1:1 (1:1, 1-0.0623)	"	"
	22	176	20°C	1:1 (1:1, 1-0.0737)	1:1 (1:1, 1-0.0652)	"	"
	21	177	20°C	1:1 (1:1, 1-0.0805)	1:1 (1:1, 1-0.0670)	"	"
	19	177	14°C	2:1 (1:1, 1-0.0863)	1:1 (1:1, 1-0.0779)	"	"
ON	5	176	35°C	1:1 (1:1, 1-0.0307)	1:1 (1:1, 1-0.0269)	"	"
	6	175	20°C	1:1 (1:1, 1-0.0321)	1:1 (1:1, 1-0.0301)	"	"
	7	176	25°C	1:1 (1:1, 1-0.0358)	1:1 (1:1, 1-0.0330)	"	"
	8	177	20°C	1:1 (1:1, 1-0.0452)	1:1 (1:1, 1-0.0380)	"	"
	9	177	15°C	1:1 (1:1, 1-0.0523)	1:1 (1:1, 1-0.0409)	"	"
	10	177	15°C	1:1 (1:1, 1-0.0499)* A (1:1 (1:1, 1-0.0455)† A	1:1 (1:1, 1-0.0419)‡	"	"
	11	176	13½°C	2:1 (1:1, 1-0.0534)	1:1 (1:1, 1-0.0449)	"	"
	17	177	10°C	Complete block	1:1 (1:1, 1-0.0449)	"	"
	19	175	35°C	1:1 (1:1, 1-0.0265)	1:1 (1:1, 1-0.0266)	"	"
	20	175	30°C	1:1 (1:1, 1-0.0288)	1:1 (1:1, 1-0.0260)	"	"
	21	176	25½°C	1:1 (1:1, 1-0.0297)	1:1 (1:1, 1-0.0293)	"	"
	22	174	20°C	1:1 (1:1, 1-0.0315)	1:1 (1:1, 1-0.0302)	"	"
	24	175	10°C	1:1 (1:1, 1-0.0352)	1:1 (1:1, 1-0.0320)	"	"
	25	174	12°C	1:1 (1:1, 1-0.0379)	1:1 (1:1, 1-0.0339)	"	"
	27	175	10°C	2:1 (1:1, 1-0.0418)	1:1 (1:1, 1-0.0334)	"	"

OOA	3	180	35 C	1:1 (4:1 - 0.0417)	1:1 (4:1 - 0.0111)	4:1 arrest, 2:1 S	Right
	4	180	30 C	1:1 (4:1 - 0.0415)	1:1 (4:1 - 0.0397)	1:1 arrest, 2:1 I	"
	5	178	25 C	1:1 (4:1 - 0.0453)	1:1 (4:1 - 0.0415)	4:1 arrest, 3:1 I	"
	7	182	20 C	1:1 (4:1 - 0.0361)	1:1 (4:1 - 0.0336)	1:1 arrest, 2:1 I	"
	8	179	20 C	1:1 (4:1 - 0.0303)	1:1 (4:1 - 0.0362)	1:1 arrest, 2:1 I	"
	9	180	15 C	2:1 (4:1 - 0.0730)	1:1 (4:1 - 0.0920)	4:1 arrest, 2:1 I	"
	10	178	15 C	2:1 (4:1 - 0.0736)	2:1 (4:1 - 0.0618)	4:1, 2:1, 1:1	"
OOB	2	154	35 C	1:1 (4:1 - 0.0673)	1:1 (4:1 - 0.0658)	4:1, 3:1	Right
	3	154	30 C	1:1 (4:1 - 0.0652)	1:1 (4:1 - 0.0600)	4:1, 3:1	"
	4	156	25 C	1:1 (4:1 - 0.0829)	1:1 (4:1 - 0.0840)	4:1	"
	5	156	20 C	1:1 (4:1 - 0.0928)	1:1 (4:1 - 0.0830)	4:1	"
	9	156	15 C	2:1 (4:1 - 0.1161)	1:1 (4:1 - 0.0999)	4:1	"
	14	152	20 C	2:1 (4:1 - 0.0367)	1:1 (4:1 - 0.0883)	4:1	"
	15	150	25 C	1:1 (4:1 - 0.0810)	1:1 (4:1 - 0.0755)	4:1, 3:1	"
	16	152	25 C	1:1 (4:1 - 0.0777)	1:1 (4:1 - 0.0743)	4:1	"
	3	158	35 C	1:1 (4:1 - 0.0262)	1:1 (4:1 - 0.0268)	Standstill of ventricle	Right
	4	156	30 C	1:1 (4:1 - 0.0233)	1:1 (4:1 - 0.0258)	"	"
	5	158	25 C	1:1 (4:1 - 0.0260)	1:1 (4:1 - 0.0273)	"	"
OQ	6	158	20 C	1:1 (4:1 - 0.0275)	1:1 (4:1 - 0.0304)	"	"
	7	158	15 C	1:1 (4:1 - 0.0431)	1:1 (4:1 - 0.0400)	"	"
	9	160	12½ C	2:1 (4:1 - 0.0465)	1:1 (4:1 - 0.0423)	"	"
	10	160	13 C	2:1 (4:1 - 0.0440)	2:1 (4:1 - 0.0425)	"	"
	11	159	13 C	2:1 (4:1 - 0.0440)	2:1 (4:1 - 0.0415)	"	"
	15	159	14 C	2:1 (4:1 - 0.0397)	1:1 (4:1 - 0.0580)	"	"
	18	159	14 C	2:1 (4:1 - 0.0376)	1:1 (4:1 - 0.0500)	"	"

¹ Heavy alternation.

² Alternation abolished.

³ Allowed to recover contacts moved and following records taken.

⁴ Right vagal stimulation 4:1 block was produced which immediately gave place to a 2:1, and often 1:1 with prolonged P-R.

A second and very similar record is shown in Fig. 2. In this record the clamp had been released from the auricle for 40 minutes, during which time complete block was always present, except when the heart was under vagal stimulation (see Table I). In this the relief of the block is more prompt, as is usual, and a 1:1 response of the appendix is established, without the interposition of a 2:1 period. Meanwhile the ventricle is brought to a temporary standstill. As the heart recovers from the effect of stimulation, the auricular block reasserts itself and the appendix again becomes motionless.

A series of observations is tabulated in Table I, where under "controlled auricular rate" the rate of rhythmic response to stimulation maintained during the whole of the corresponding observation is given. In the next two columns conduction from auricle to appendix before and during vagal stimulation is indicated by the ratio of the rates, and in the case of 1:1 response by the transmission intervals (*A-I*). In the succeeding columns the vagus used and the strength of stimulation are indicated. In the last column but one the degree of *A-I* block resulting from vagal stimulation is noted. In the last column the relation of the observation to the application or release of the clamp is indicated. Most of the observations were made immediately after the first application of the clamp, or after its release and re-application.

Atropine and acetyl-choline. That the effect on the auricular block is a true vagal effect and is not due to escape of current to the sympathetic has been fully determined. The vagus (right and left) was stimulated high in the neck in all instances: in two experiments (Dogs NY and OB), after repeatedly obtaining release of the appendix from a condition of persistent complete block, atropine was injected intravenously, without reapplying the clamp. The reaction was in each case destroyed by this injection, the adequacy of which was shown by the simultaneous disappearance of vagal block at the *A-V* ring. More recently instead of faradising the vagus, we have used acetyl-choline to stimulate it, and have obtained an identical reaction, namely, release of high grades of block produced by clamping.

Observations on block produced by cooling.

We first attempted to obtain intra-auricular block as a result of cooling, by means of a specially constructed cooler. The apparatus consisted of a small circular box of brass, flat on its upper and lower surfaces and having a circular hole cut through its centre to expose a corresponding area of muscle to view when the box lay flat on the auricular wall. The sides of this hole were sealed off with metal, so as to convert the rest of the box into a closed and hollow brass ring; into the latter, inlet and outlet tubes were soldered, and through these water at various temperatures could be passed. Thus, a central area of muscle could be examined while the surrounding ring of muscle could be cooled at will. It was hoped that by passing water sufficiently

cold through the ring, a block between outer and inner muscle could be induced, while the former responded to rhythmic stimulation. This procedure was not successful, however, for in only one out of a number of experiments could such block be obtained. The difficulty, so it was judged, was that deep muscle fibres were apt to escape cooling on one or other side of the ring. The method was abandoned.

Eventually we succeeded by using again the base of the appendix. With a powerful clamp the muscle bounding the deep surface of the appendix at its base was crushed and destroyed, and this line of crush was prolonged on to the superficial surface of the appendix, so that only a small bridge of muscle, $\frac{1}{2}$ to 1 cm. across, joined the body of the auricle to the appendix itself. A flat lead tube was laid on this bridge, and water, at various temperatures, was passed through it. Pairs of contacts were arranged, as in the previously described experiments, one on the appendix and one on the body of the auricle, and the auricle was stimulated in line with these.

Effect of cooling. Records were taken while the water was at body temperature, and at temperatures varying from this down to 10° C., the water being allowed to circulate for 2 minutes on each occasion. The transmission interval is on occasion found to rise when the temperature falls below 30° or 25°, usually, when it falls below 20°. This rise of interval increases until a temperature of about 15° is reached, when, if the auricle is beating at rates of about 150-180 per minute, 2:1 response appears (see Table II). Before the appearance of 2:1 response, the transmission interval has risen by approximately 50 per cent. On one occasion, complete block was seen at a temperature of 10°.

Effect of vagal stimulation. The right nerve has alone been tested. When an effect is produced, it is uniformly expressed as a reduction in the degree of the preceding block. The instance of complete block and most instances of 2:1 block could thus speedily be reduced to a condition of 1:1 response. The reaction, however, takes place after a rather longer delay than is the case with compression block. When, under cooling, a 1:1 response, accompanied by a prolonged transmission interval, prevails, vagal stimulation reduces the length of this interval. Where the original prolongation is slight, under the influences of the vagus it becomes normal again. Where the prolongation is greater, the interval is very decidedly reduced but does not return to the normal figure.

In some experiments, however, especially in those where temperatures of 14° C. and lower are being used, no decided effect may be witnessed upon stimulating the vagus. This can be seen from Table II, when in the 2:1 block stage, vagus stimulation fails frequently to relieve the block, or to show any material reduction in the transmission intervals.

It is to be remarked that we are also cooling nerves and nerve endings, and that the cooling must spread into the muscle surrounding the lead tube,

and that this failure to elicit a reaction to vagus stimulation may be due to a consequent local failure of the nerve endings. That spread of cooling is taking place is indicated by the intrinsic deflections, given by the distal electrodes, placed upon the tip of the appendix. These intrinsic deflections, as the temperature in the tube is lowered, begin to lose their original form, present a much less sharp rise and fall, and a smaller amplitude; suggesting that changes are taking place both in the systole of the muscle underlying the electrodes and in conduction; alternation is frequently met with while these changes are progressing, and such alternation is abolished by vagal stimulation.

Fig. 3 shows a record of a 2:1 block passing into a 1:1 response under vagal stimulation. The top curve (*APP*) is an electrogram from the appendix distal to the clamp, and the bottom curve (*AUR*), from the body of the auricle proximal to the clamp. At the beginning of the record, water at a temperature of $12\frac{1}{2}^{\circ}\text{C}$. has been flowing through the tube for 2 minutes, and the body of the auricle is responding to rhythmic shocks at the rate of 159 per minute, and gives rise to the sharp deflections of the lower curve; the ventricle is responding to the auricle and is recorded as small deflections (*r*) in the lower curve. The tip of the appendix is responding to every alternate stimulus, and gives rise to the deflections in the upper curve (which are less sharp than in the lower curve). The vagus is then stimulated just after beat 1, and the ventricle is brought to a standstill, and shortly afterwards, from beat 8 onwards, the appendix responds to every stimulus.

Although in these effects the vagus was stimulated high up in the neck, it seemed desirable that this result of vagal stimulation should be confirmed by the injection of acetyl choline: sufficient acetyl choline was injected to produce a complete ventricular standstill, and in this way also the 2:1 block was relieved several times.

Discussion.

The observations here recorded were largely prompted by previous work in which the conclusion has been reached that the vagus has no effect on the rate of *fibre* conduction in the normally beating auricle, but that when, in special circumstances, conduction through the muscle sheet is impaired, vagal stimulation is capable of restoring normal conduction. Impairment of auricular conduction, consequent on a high rate of beating, or after the administration of such poisons as strophanthin and quinidine, is relieved partially or completely by vagal stimulation. This effect has been ascribed to the power of the vagus to reduce the length of the refractory period of the auricular muscle, an increase of the latter being in the circumstances largely or wholly responsible for the originally defective conduction. By provoking intra-auricular block, either by pressure or by cooling, we had hoped to add further examples of a parallel kind, and thus to establish our conclusions on a more general basis.

The first anticipation has not been disappointed, for both by pressure and by cold, block may be produced in its several degrees in the auricular muscle; and these blocks, like those previously dealt with, are cleared away in part or in whole by vagal stimulation. This result was anticipated, because it was thought probable⁷ that compression and cold might induce block, either by prolonging the systole of the muscle, and thus lengthening its refractory period, or by depressing excitability. The second hope, that our former conclusions might be made general, has not been fulfilled completely.

Prolonged conduction intervals and 2:1 response might be explained on the basis of a prolonged refractory period, or by a lowered rate of recovery of excitability, when they are produced by cold or pressure. A relief of blocks, so arising, by vagal stimulation could be explained reasonably, by supposing a reduction of the refractory period with its consequent lengthening of the period of recovery. But we have encountered unexpectedly the fact that complete block, produced by the same means, is also relieved. The case which presents the greatest difficulty is that of complete block produced by pressure. In this instance, the muscle pressed upon may refuse to conduct for very long periods, extending to as long as 40 minutes and persisting long after removal of the clamp. The muscle is not dead, for it will recover after this long period of quiescence; neither is it rendered temporarily and wholly incapable of functioning; for if at any time during this period the vagus is stimulated the obstruction to the passage of impulses is removed for the period of stimulation. The remarkable fact remains that the functions of the compressed muscle appear to lie dormant for considerable periods of time, and that the vagus is capable of throwing them once more into activity. To explain blocks of this kind as resulting from lengthened refractory period, and their removal by the vagus as due to the shortening of the refractory period, would involve two distinct assumptions; firstly, that severe pressure can produce a contraction in muscle of inordinate duration, a form of prolonged standstill in systole, and, secondly, that vagal stimulation is capable of reducing the length of a systole during its progress. In regard to the last assumption, we know of neither supporting nor conflicting evidence; but the correctness of the first assumption appears so improbable that, for the moment at all events, it must be placed on one side.

A curious and paradoxical acceleration of the whole heart occurring in special circumstances and under vagal stimulation has been recorded by Dale, Laidlaw and Symons¹: they inclined to attribute it to the presence of normal cardiac accelerators in the vagus as opposed to sympathetic fibres, their idea being that the effect of stimulating these accelerator fibres is normally overshadowed by that of the inhibitor fibres. They regarded the condition of their experiments as producing a depression of the inhibitory fibres, thus revealing the accelerator effects. The reactions which we have described are not susceptible to a like explanation; for they are invariably

accompanied by a profound inhibitory action upon other parts of the heart ; when the local block at the base of the appendix is relieved, a high grade of block is simultaneously manifested at the A-V junction and, as is readily seen in the experiments, the auricular contractions diminish almost to the point of invisibility. Thus it is quite clear that the inhibitory vagal fibres are exercising their usual profound influence upon the heart as a whole, at the instant at which the block is relieved in the appendix ; and we are consequently indisposed to accept the view that the local effect results from a selective action of accelerator vagal fibres, which might be supposed to exist. It appears to us that we have to deal with a normal vagal impulse, playing upon muscle in which the conditions are peculiar : and that this local peculiarity of the muscle fibres (consequent on pressure or cooling) is responsible for the effect witnessed. We go farther and suggest that the phenomenon brought to light in this fashion may be the revealing of normal effects of vagal governance of the heart, effects always present but usually concealed. It is to be emphasised that we are not able to exclude an action comparable or analogous to that previously described, where a reduction of the refractory period of the muscle produces an apparently paradoxical effect : but given that such an explanation is inapplicable to the present effects, then we are thrown back upon more fundamental inferences. Gaskell⁶ was wont to lay stress upon the anabolic effect of vagal stimulation. Of the precise view which he held we feel uncertain. It is clear, however, that he intended to express an activity contrary in its direction to that displayed as a depression of function, and that he considered the vagus may be responsible for a building up and storing of energy, though its activity is chiefly displayed in preventing the dispersal of energy. These ideas of his do not appear at any time to have gained wide acceptance, and some of the arguments which he used to support them have since weakened. The most notable instance of this weakening of evidence is to be found in Einthoven's² recent explanation of Gaskell's experiment,⁶ in which he described a positive variation of the demarcation current under vagal stimulation. Gaskell regards the nerve supplying a somatic muscle as katabolic, and the vagal supply of the heart as anabolic : he instances the positive variation produced by the vagus in contradistinction to the negative variation of the demarcation current produced by the somatic nerve. It seems probable from Einthoven's observations that this positive variation, induced by vagal stimulation, is non-existent. That being the case, we are led to inquire if evidence from other sources supports the view that vagal stimulation leads to a building up and storage of energy, while at the same time it impedes its dispersal in the form of muscular activity. Of a storage there is evidence ; of a building up which is more intense than normal, there is little evidence that is clear. Yet, because this evidence is unclear the hypothesis cannot be placed altogether on one side : it might be used to explain the phenomena which we have been describing. Our suggestion is that in the circumstances of our own experiments the vagal influences

which may be exerted normally upon the energy of the muscle, namely, an increased storage on the one hand and a diminished dispersal on the other, become locally dissociated; that the first is retained and that the last is decreased or abolished. A parallel explanation appears to us to be applicable to the phenomena described by Dale, Laidlaw and Symons, as an alternative to that put forward by these workers.

CONCLUSIONS.

1. Block in varying degrees can be produced between different portions of the auricular muscle of the dog by applying pressure or cold.
2. The blocks so produced are abolished in part or in whole by stimulating the vagus, while simultaneously the inhibitory nerve influence is displayed at the *A-V* junction by the production of block.
3. The meaning of this paradox is discussed.

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Fig. 1. (Dog XX, record No. 22.) *VM*, ventricular myogram; *APP*, right appendicular lead; *1/5*, auricular electrogram. Complete block between the auricle and appendage, readily produced by clamping the base of the appendage, is relieved by stimulating the right vagus. The vagal stimulation produces standstill of the ventricle. Time limits of a second in this and the remaining records.

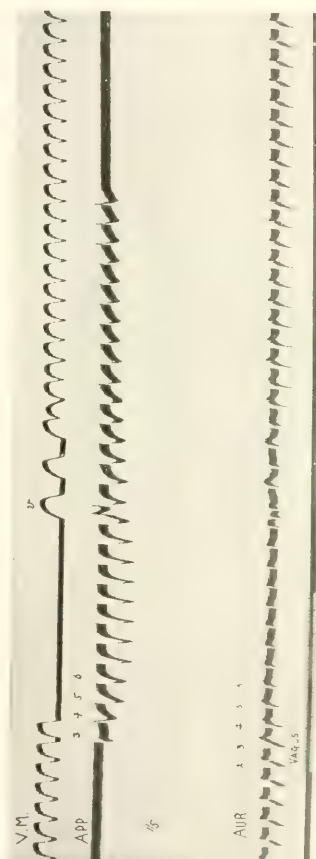


Fig. 2. (Dog XY, record No. 17.) A singular record, showing the relief of complete block by right vagal stimulation, and the subsequent reappearance of complete block. The record was taken 10 minutes after releasing the clamp.

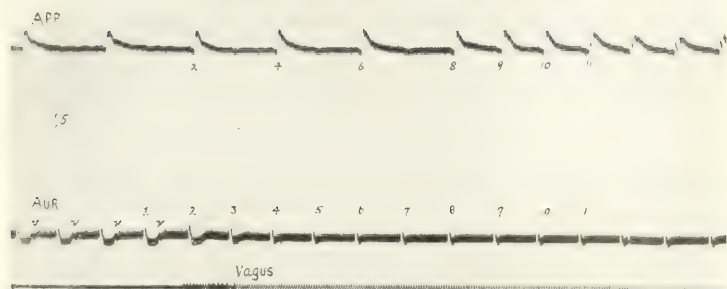


Fig. 3. (Dog OQ, record No. 9.) *APP.*=appendicular and *AUR.*=auricular electrogram. 2 : 1 block between auricle and appendix has been produced by cooling the base of the appendix to $12\frac{1}{2}^{\circ}\text{C}$. Right vagal stimulation soon converts the 2 : 1 into a 1 : 1 response, which continues to the end of the record.

"A CASE OF HEART BLOCK ILLUSTRATING THE BEHAVIOUR OF THE AURICLE DURING PERIODS OF PROLONGED VENTRICULAR SILENCE."

By HAROLD WILTSHIRE.

(*Department of Cardiology, King's College Hospital.*)

THE chief interest of this case centres in the behaviour of the auricle during periods of prolonged ventricular inactivity, as revealed by electro-cardiograms which show the whole course of several complete attacks.

Clinical notes.

M., a man, age 63, was admitted to King's College Hospital at 6.0 p.m., on June 29th, 1922, complaining of attacks of "flatulence which sets up heart trouble."

History. The family history was unimportant. The patient had led an active life as a shopkeeper and, save for some indefinite dyspepsia of recent years, had enjoyed good health, his only illness having been a single attack of severe tonsilitis which occurred so many years ago that the exact date could not be remembered.

The first syncopal attack occurred three years ago, at a time when he felt perfectly well. When out for a walk he suddenly "came over dizzy" fainted, and fell down. In falling he "broke the bone of his cheek." He thinks he was unconscious for about 10 minutes. After a week in bed with no further symptoms he felt quite well again, "able to do anything," and he remained in perfect health until August, 1921, when a second attack occurred. This seems to have been like the first but less severe. After this he remained quite well until five weeks before admission, when a third attack of the same nature occurred. He was kept in bed three days but then appeared quite well again. A fortnight later, however, *i.e.*, three weeks before admission, he had another attack which proved to be the first of a series. At first these occurred about once a day, but their frequency increased, the patient stating that they had been "very numerous" during the last three days, and had prevented him from getting any sleep. According to his wife they had occurred at intervals of about 10 minutes throughout the 24 hours before admission. She described them as "fainting fits" in which consciousness was completely lost and she had noticed that twitching movements of the limbs occurred during some attacks. The patient himself was not aware that loss of consciousness was complete. Except for a little headache, he complained of no pain, and he himself regarded flatulence as his most distressing symptom.

Condition on admission. The patient was a well nourished man of normal appearance and mental condition, who looked rather younger than his age.

The pulse was regular, 26 per minute, of full volume. The artery wall appeared normal. The systolic blood pressure was 180 mm. Hg. Auricular

venous pulsation was visible in the neck, about 100 per minute. The chest wall was thick and the apex impulse could not be seen or felt. On percussion relative cardiac dulness extended for half an inch beyond the left nipple line. On auscultation a loud blowing systolic murmur was heard. This was most intense in the mitral area, poorly conducted into the axilla, and audible with diminishing intensity up to the base. The second sounds at the base were of normal quality, but faint. The lungs, mouth, abdomen and central nervous system gave no sign of disease. No urine was passed during the first 24 hours in hospital. The bladder, which only contained about six ounces, was then emptied by catheter a concentrated specimen being obtained which contained a rather heavy cloud of albumen. This oliguria and albuminuria was thought to be due to the inefficient circulation through the kidney. The Wassermann reaction was reported as "negative but not quite clear."

An electrocardiogram confirmed the clinical diagnosis of complete heart block. The auricular rate was 100 per minute, and that of the ventricle 22 per minute. The ventricle was not quite regular in time. The ventricular complexes indicated well marked left side preponderance with some slight delay in ventricular conduction, the *Q*, *R*, *S*, time being 0.12 of a second. The *T* wave was well marked, and was upright in all three leads.

At the time of admission syncopal attacks were occurring at irregular intervals, about one every ten minutes, and were of varying duration up to about half a minute. At the start of each attack respiration became slow, deep, and sighing, but as the attack progressed it quickened steadily, at the same time becoming more shallow. The face turned slightly pale and cyanosed, but this change in colour was remarkably slight. The eyes were rolled upwards. Consciousness was rapidly lost. After some fifteen seconds twitching movements began in the hands which were jerked up towards the mouth as if the patient were trying to fumble with his teeth, the head at the same time being bent forward as if to meet the hands. With the first returning pulse wave a single deep sighing respiration was taken; the head fell back and the hands fell to the side and either remained still or gave one or two spasmodic movements: colour was rapidly restored in the face; and after a short period of apnoea normal respiration was resumed. From the patient's manner and speech it was evident that he did not realise that loss of consciousness had been complete.

Course in hospital and termination. The subsequent story is one of steady increase in frequency and severity of attack, little, if at all, modified by attempts at treatment.

By 9.0 p.m., within three hours of admission and before any drugs had been given, the attacks were more severe and the intervals between them were reduced to some five minutes. At 9.30 p.m. atropine sulphate gr. 1/100 was given by hypodermic injection, and this producing no effect, another dose, gr. 1/50 was given an hour later. This seemed to

do good, and the patient slept quietly for half an hour. Attacks then recurred again until 2.0 a.m. when he again slept for 40 minutes. At 2.40 a.m. a series of 8 attacks occurred within 5 minutes and another dose of atropine (gr. 1.50) was given. The attacks, however, continued unabated, and the patient became very restless, struggling and trying to get out of bed. At 3.30 a.m. a hypodermic of morphia (gr. $\frac{1}{4}$) was given, and this was followed by a quiet period for half an hour. Then the attacks recurred again as before, but the patient no longer regained consciousness between them.

From this time until death occurred some 36 hours later consciousness was never regained, and the patient remained in an almost continuous "status" of attacks, one following after another with barely sufficient time between for the circulation to be kept going. The periods of ventricular activity and silence were, in fact, roughly of equal length.

The duration of individual attacks varied but showed some relation to the previous rate of the ventricle. When the ventricle was slow, about 22 per minute, the subsequent attacks were likely to be short, lasting about half a minute; but when the ventricle was rapid, about 60 to 80 per minute, the subsequent attack was likely to last a minute or more, several being noted which persisted for over 100 seconds.

After a little observation it became possible to know what the ventricle was doing by simply watching the patient. Cessation of ventricular action was signalled at once by deep, slow, sighing respirations, which steadily increased in rate and became more shallow as the attack progressed. After about 30 seconds the mouth was closed and respiration became more noisy. The colour of the face gradually changed to a muddy pallor tinged by slight cyanosis, but this change was remarkably less than one would have expected. The moment a ventricular contraction ended the attack respiration ceased completely and there was a period of apnœa lasting some 10 seconds, during which a vivid bright pink blush spread all over the face and neck. Respiration was then resumed and the pink blush faded quickly, normal colour being regained. Up to the time when morphia was given, twitchings and spasmodic movements of the limbs were a constant, though by no means prominent, feature of all attacks, which lasted over 15 seconds. After the morphia, however, this convulsive tendency became much less; in fact, in many of the later attacks the limbs remained completely motionless, thus making it possible to obtain complete electrocardiographic records.

Some 6 hours before death occurred, at a time when the ventricular rate was persistently high, and the attacks in consequence were prolonged and severe, an injection of morphia (gr. $\frac{1}{4}$) and atropine (gr. 1.100) was given. At the time this appeared to do a little good, as it was followed by a fall in ventricular rate, and some reduction in length of attack. When, however, the same injection was repeated later, with the same object, it produced no effect.

About 3.0 p.m. on July 1st, a very severe attack occurred, the nurse reporting that the pulse had stopped for two minutes before I reached the bedside. The patient was lead grey in colour and appeared to be dead, but after a few acts of artificial respiration natural breathing was resumed, and, a few seconds later the ventricle started to beat again. About an hour later, however, another prolonged attack occurred, and this proved fatal.

Post-mortem.

General. The lungs were slightly emphysematous. Small old tuberculous scars were present at both apices. Both lungs showed general œdema and hypostatic congestion at the bases, and there were numerous submucosal petechial hæmorrhages in both bronchi. The kidneys were normal to the naked eye, but showed slight increase of interstitial tissue on microscopic examination. The brain was normal except for some slight venous congestion. A small psammoma was present in the left lateral ventricle, attached to the choroid plexus by a thin pedicle. Except for these changes the organs in general were normal.

Cardiovascular. The heart was somewhat enlarged owing to dilatation of the right side, and hypertrophy of the left ventricle. There was a good deal of subpericardial fat and the coronary veins were distended with venous blood. The right auricle and ventricle were dilated and filled with dark venous blood and post-mortem clot. The pulmonary and tricuspid valves were normal. Nothing abnormal could be seen or felt in the region of the junctional tissues. The main mass of the left ventricle appeared normal in colour and consistence, but in one or two places small patches of lighter colour, were present. It was thought that these might be due to fatty degeneration, but microscopic examination was negative. One minute subendocardial petechial hæmorrhage was present about half-way down the septal wall of the left ventricle. Small early atheromatous patches were present in the first part of the aorta, and on the aortic cusps and mitral valve flaps, but these changes were not considered more than is usual at the age of the patient. The coronary arteries showed atheroma to a more marked degree, with considerable calcareous deposit, but in no place was the lumen of the main trunks narrowed to a serious degree.

Microscopically. the general heart muscle showed very well marked brown atrophy, but in other respects appeared normal. Serial sections were cut of the junctional tissues. The tissue of the A-V node and of the upper part of the main bundle appears fairly normal. There is, perhaps, a slight relative fibrosis of the tissues around the bundle, but this change is not marked and could not have affected function. Just above the point of division of the main stem, however, there is a comparatively abrupt change, the bundle becoming markedly fibrosed. The overgrowth of interstitial connective tissue is so great that the bundle might be described as a fibrous cord containing a few strands of muscle fibre. The fibrous tissue infiltrated between and isolated the few remaining muscle fibres from one another. It is well formed and there is no evidence of active cell proliferation or recent development of new connective tissue. This fibrosis involves the termination of the main bundle, and, in lesser degree, the beginnings of its two main branches. The few remaining muscle fibres vary in size. Some appear swollen and degenerate, but it is difficult to judge of the ante-mortem condition of their cytoplasm in a paraffin section.

The small arteries of the part show slight thickening and intimal proliferation, but this change is not marked and does not appear sufficient to account for the extreme fibrosis in the lower end of the bundle. A few small areas of calcareous deposit are present in the base of the aorta, and one small focus of similar deposit is present near the bundle at the top of the muscular interventricular septum.

Electrocardiographic observations.

Complete electrocardiograms were obtained of several attacks in which ventricular silence persisted for periods varying in duration from 12.6 seconds up to 67 seconds. In seven of these the attack lasted over a minute. These records are unfortunately much too long to be reproduced in full, and only small sections can be given in illustration of particular points*: but the sequence of events of each attack is indicated in Table I. At the time when two of these attacks were registered (Nos. 15 and 16) the auricle was in state of flutter.

These electrocardiograms indicate that the auricle suffers considerable distress during periods of prolonged ventricular silence, for though auricular contractions of normal type continue for some time after the ventricle has ceased to beat, they fail sooner or later, and, for the rest of the period of ventricular inactivity the action of the auricle is uncertain and deficient. The changes in auricular action may be considered in their order of sequence in the attack.

(a) *The phase of persistence of auricular contractions of normal type.* Reference to Table I will show that in some attacks auricular action of normal type persisted for a comparatively long period (over 40 seconds), whereas in others a change took place much more early (about 20 seconds). In this respect two classes might be recognised, one of late auricular failure, and one of early failure, and it is perhaps a suggestive fact that the class of early failure occurred in the later attacks when, presumably, the auricle was more exhausted. The class of late failure is represented by the three first prolonged attacks registered, Nos. 2, 3 and 4, and in these the normal type of action persisted for 44, 42, and 42 seconds, respectively. All the later attacks belong to the class of early failure, normal action ceasing, on the average, at the end of 19.4 seconds (maximum No. 13, 27 seconds, minimum No. 19, 13.5 seconds). No progressive decrease of the duration of normal action can be discerned; the first example of the class of early failure being registered within some twenty minutes of the last attack showing late failure. In two attacks, Nos. 15 and 16, the auricle was in a state of flutter, and in these the flutter mechanism persisted throughout, though not without alteration, as detailed later.

During the first ten seconds after the ventricle has ceased to beat the auricle usually shows but little change. After this it tends to quicken slightly and to maintain a more rapid rate for some ten to fifteen seconds. This, however, then gives way to progressive slowing, the original rate being reached again in about half a minute, after which slowing progresses still more rapidly until a speed is reached considerably (some 20 beats per minute) below that at the commencement of the attack (see Fig. 1).

* In all illustrations the lead shown is Lead II. The sensitivity is standard. 3.2 Sensitivity was purposely increased in order to bring out the action of the auricle.

TABLE

Grm. No.	Date and time.	RATES BEFORE ATTACK.		Duration of attack in secs.	AURICLE DURING ATTACK.		
		Auricle.	Ventricle.		Rate before failure of normal mechanism.	Time of transition	After failure of normal mechanism.
1	June 29 8.45 p.m.	100 regular	25 regular	12.6	Steady increase of rate to 110	---	---
2	June 30 2.30 p.m.	108 regular	27 slowing at end	46	1st 10" — 108 2nd 10" — 120 3rd 10" — 114 4th 10" — 102 Last 4" — 90	44th sec.	3 ectopic beats in 2"
3	2.40 " p.m.	111	30 slowing at end	53	1st 10" — 114 2nd 10" — 120 3rd 10" — 114 4th 10" — 96 Last cycle — 85	42nd sec.	Very irregular slight ? ectopic deflections
4	"	115	48 slowing at end	67	1st 10" — 103 2nd 10" — 114 3rd 10" — 103 4th 10" — 93 Last cycles — 81	42nd sec.	Irregular for 10", then questionable
5	5.15 " p.m.	120	47 slowing at end	63	1st 15" quickens 122 to 130 Last 6" slows to 125	21st sec. abrupt	1st-10th sec.—ectopic rhythm. 10th-25th sec.—more normal type. Slowing 107 to 88. Last 15"—auricular silence.
6	3.30 p.m.	122	54 slowing at end	58	Practically regular. 122-124 per min.	21st sec. abrupt.	1st-25th sec.—slow, irregular, ectopic. Last 12"—auricular silence.
7	5.30 p.m.	125	56 slowing at end	63	Practically regular. 125-127 per min.	18th sec. abrupt.	Very slow, irregular, ectopic and ? normal type.
8	5.35 p.m.	130	60 slowing at end	61	130	17th sec. abrupt.	Silent except for irre- gular slow beats. Some ectopic. These apt to occur in pairs
9	5.50 p.m.	125	50 slowing at end	46	Practically regular. 126	19th sec. abrupt.	1st 20 secs. slow, irregular, from var- ious foci. Last 7" slow normal type at 53 per min.
10	7.45 p.m.	120 ?	54 slowing at end	63	Quickens 120-125	19.5 sec. abrupt.	1st 8 secs. irregular, normal and ectopic. Then normal type about 50 per min.

I.

AFTER ATTACK.					REMARKS.
AURICLE.		VENTRICLE.			
Recovery takes	Subsequent rate.	1st cycle length in secs.	R-T interval in secs.	Subsequent rate.	
—	—	—	—	—	Convulsion during attack, obscures later events.
1'	1st 8'' quickens 95 to 111. Then regular.	2.74	Before 0.64 After 0.78	30 per min.	
5'' after one or two doubtful ectopic beats.	1st 10'' quickens 100 to 120	2.8	Before 0.63 After 0.84	Quickens to 48. Then slows again.	After 49 secs. ventricular activity continued in gram 4.
4'' after two slow ectopic beats.	—	2.34	Before 0.44 After 0.78	—	Direct continuation from gram 3. Ends before subsequent rate of auricle and ventricle is registered.
5'' after two ectopic beats.	Starts 71, quickens rapidly.	10.4	Before 0.44 After 0.63	Rapidly quickens to 60	
5''	Starts 88, quickens rapidly.	2.72	Before 0.60 After 0.68	Rapidly quickens to 68.	
8'' Low deflections after 2''.	115	4.6	Before 0.44 After 0.72	Rapidly quickens to 60	
5'' after two slow ectopic beats.	92 increasing to 115 within 6''.	3.12	Before 0.48 After 0.76	Rapidly quickens to 60.	
4.2'' after one ectopic beat.	105 rapidly quickens to 124.	2.44	Before 0.61 After 0.72	First few slow. Later 32.	
6.5'' after one or two ectopic beats.	85 quickening rapidly to 120	3.0	Before 0.56 After 0.92	First few slow. Later 56.	

TABLE I

Gm. No.	Date and time.	RATES BEFORE ATTACK.		Duration of attack in secs.	AURICLE DURING ATTACK.		
		Auricle.	Ventricle.		Before failure normal mechanism.	Time of transition	After failure normal mechanism.
11	8.10 p.m.	122	40 slowing at end	31.4	Regular 125	19th sec. abrupt.	Single ectopic, then 2 ^{1/2} silence, then ectopic 50 per min.
12	8.30 p.m.	115	19 per min.	49.5	1st 10" 115 2nd 10" 120 Last 6" 111	26th sec. abrupt.	3" silence, then slow irregular ectopic or normal beats.
13	"	118 slowing to 111	Slow couples.	68.3	Starts 111. Quickens to 120. Then slows to 115.	27th sec. abrupt.	Starts 7" silence broken by 1 ectopic. Then irregular, ectopic or normal, about 48 per min.
14	8.40 p.m.	123 ?	58 per min. last few slow.	62.2	Starts 122. By 15" quickens to 130. Then starts to slow.	20.5 sec. abrupt.	4.5 sec. silence. Then ectopic, 56 per min. for 14". Then irregular normal type.
15	" 11.30 p.m.	Flutter at 250 per min.	56 slowing at end.	36.2	Flutter continues throughout. 1st 10" at 238 per min. 2nd 10" " 186 " 3rd 10" " 186 " Last 6" " 180 "		
							} With steady diminution in extent of deflection.
16	"	Flutter at 250 per min.	56 slowing at end.	51	Flutter continues throughout. 1st 10" at 240 per min. 2nd 10" " 186 " 3rd 10" " 180 " 4th 10" " 174 " 5th 10" " 164 " 6th 10" " 165 "		
							} With steady diminution in extent of deflection and appearance of some irregularity.
17	July 1st 1.0 a.m.	130	70	55 + gram ends.	Quickens slightly, 130 to 136	15th sec. abrupt.	4 doubtful transition beats. Then ectopic rhythm slowing from 36 to 52, and then gradually quickening again.
18	8.15 a.m.	?	64	74 gram ends.	Quickens 125-135	15th sec. abrupt.	3" auricular silence. Then slow irregular ectopic or normal type.
19	8.25 a.m.	?	64	12.5	Quickens 133-142	13.5 sec. abrupt.	Slow, irregular ectopic beats, about 72 per min.

(continued).

AFTER ATTACK.

AURICLE.		VENTRICLE.			REMARKS.
Recovery, takes	Subsequent rate.	1st cycle. length in secs.	R-T interval in secs.	Subsequent rate.	
3" after one or two ectopic beats	111 quickening steadily to 120	3.8	Before 0.66 After 0.72	33 per min.	*Last ventricular cycle before this attack = 9 secs.
5" after one or two ectopic beats	Starts 103. Quickens to 118. Then slows to 111.	3.64	Before 0.60 After 0.84	30 per min., later slow couples.	Continued direct in gram 13. Intervening period of ventricular activity = 53.5 secs.
7" after 3 or 4 ectopic beats.	Starts 100, quickens steadily	2.96	Before 0.50 After 0.84	Starts slow, quickens to 40.	
6" after 3 or 4 ectopic beats.	Starts 74, quickens rapidly.	2.96	Before 0.52 After 0.80	Starts slow, quickens rapidly to 57.	Shows a whole period of ventricular activity. 54 secs.
See remarks.	See remarks.	See remarks.	?	See remarks.	At 36.2" of attack single ventricular beat occurs followed by further silence for 10 secs., after which gram obscured owing to patient moving. Within 5 secs. of this single beat flutter rate recovers from 187 to 230.
Within 2" some recovery rate. Within 4" rate rises to 214.	Not shown. Gram ends.	?	?	Not shown.	
Gram ends					End of attack not registered.
Gram ends					Gram ends after registering 74 secs. of ventric. silence
5" after one or two ectopic beats	Not shown.	2.88	Before 0.42 After 0.64	Not shown.	

These changes were observed in the three earlier attacks, those classed as late failure. In all the subsequent attacks, which are classified as early failure, the same tendency to initial quickening was seen, but transition to an abnormal mechanism occurred before the subsequent slowing could become established.

Coincident with the slowing in rate of the auricles there was a change in the auricular deflections. This change is seen to be a gradual decrease in amplitude of deflection which becomes more obvious as the slowing becomes more marked. The auricular deflection, in fact, appears to be fading away (see Fig. 1). In the later grams of early failure, in which slowing could not become established this gradual failure of deflection is not seen. It is, however, represented, the last beat or two of normal type always showing some decrease in the extent of the deflection and a more blunt outline.

It is interesting to note that these two alterations, reduction of speed, and decrease in amplitude of deflection, are also represented in the two attacks which occurred while the auricle was in a state of flutter. In flutter, however, no initial quickening occurs, in fact reduction in rate appears to be progressive from the start. A fall in from 240 per minute to 164 per minute occurred in one attack lasting a minute (gram 16); and a rate of 168 per minute occurred at the end of another attack, the beginning of which was missed (see Figs 5 and 6).

Simultaneous with this slowing of the flutter there is a progressive alteration in deflection, as will be seen in Fig. 5, A. the normal outline, given by each cycle of flutter consists of a fairly rapid upward deflection ending in a sharp peak. This is followed by a more gradual return, flattened about half way down the descent by a brief pause, and ending in a fairly sharp downward peak. During the attack, as the action became slow, these curves tend to become slightly irregular, the extent of the deflection is reduced, the sharp peaks become more blunt, and the pause on the descending arm becomes a low, secondary, upward deflection, which at times forms quite a sharp little peak (see Fig. 5, C, and Fig. 6).

(b) *The transition to an abnormal mechanism.* Following the changes mentioned above there is an alteration in the mechanism of the auricular beat. When, as in the type of late failure, previous decrease in rate and extent of deflection have been marked, these later appear to lead up steadily to the change in mechanism, but in all the later grams of early failure type the transition is comparatively abrupt.

(c) *The phase of abnormal action.* The appearances seen during this phase vary so much in different attacks, and at different times during the same attack, that it is impossible to describe one as more characteristic than another. The most usual event may be described as a mixture of the following :—

(1) The auricle may remain completely inactive for short periods. Short intervals lasting three or four seconds, without any sign of an auricular

activity are not rare, and more prolonged periods may occur. In gram 5 the appearances indicate that the auricle was completely silent for the last 13 seconds of the attack, and for the first four seconds after the attack ended (see Fig. 4), a total of 17 seconds in all; and again in gram 6 it would appear that a similar period of 15 seconds of complete auricular inactivity occurred at the end of the attack. Certain low blunt deflections which occur during these periods I believe to be due to respiration, firstly, because they are unlike the deflections caused by any cardiac event and, secondly, because they can be traced out as numbers of a series which continues throughout the whole period of ventricular silence. This series shows a steady increase in rate, and is abolished when the attack ends, thus corresponding exactly with the respiratory events of the attacks as recorded in the clinical description above.

(2) Short periods may occur in which the auricle seems to resume slow action initiated from a focus at, or near, the normal site. When this occurs, the rate, as compared with the previous normal, is always much reduced, and the deflections, though upright, are of low amplitude. In gram 10 an interesting instance of this type occurred in which the rate averaged 50 per minute, but showed alternate long (1.24 seconds) and short (1.04 seconds) cycles.

(3) Similar short periods may occur in which the auricle gives a series of contractions initiated from an obviously ectopic focus. An example of this mechanism is seen in Fig. 3 (gram 17). In the attack from which this is taken the normal mechanism failed at the end of 15 seconds. The ectopic rhythm commenced three seconds later and persisted for 37 seconds, when the gram ended, so that it could not be followed further. During the first 20 seconds of this ectopic rhythm the rate slowed steadily from 86 to 52 per minute, but in the ensuing 10 seconds it quickened again to 86. The persistence of any single type of rhythm for as long a period as this was distinctly unusual.

(4) Complete irregularity of the auricle, both as regards time and type of complex seen, is perhaps the most common event during the phase of abnormal action (see Fig. 2). At irregular intervals slight deflections occur, some of which imitate the normal in that they are upright, while others copy the ectopic type by being inverted. The impression given is that of an auricle contracting in response to any focus which can muster sufficient energy to produce a stimulus.

(d) *The recovery of the auricle.* When the ventricle starts to beat again the auricle recovers and resumes normal action almost at once. Usually the first ventricular contraction is followed by one of two irregularly spaced auricular beats from an ectopic focus, but then, on the average within 4.5 seconds of the end of the attack, the first of a series of normal auricular

contractions occurs. This series begins at a slow rate (average 95 per minute) but quickens steadily and rapidly. Recovery of the deflection's amplitude begins at once and is very rapid, being accomplished within a few beats (see Fig. 1). Even a single isolated contraction on the part of the ventricle can succeed in restoring the auricle. Thus in gram 5 (see Fig. 4) an isolated ventricular contraction, which occurred after 63.5 seconds of silence, was followed by a further 10 seconds of silence. Though the auricle had been completely out of action for 13 seconds before this ventricular beat, two ectopic auricular beats occurred within 3 seconds after it, and the normal auricular mechanism was restored before a second ventricular contraction occurred.

Similar indications of auricular recovery at the end of the attack were also seen when flutter was present. Fig. 6 illustrates the end of the attack which preceded that registered in gram 16. During the attack, the length of which is not known, the flutter rate had fallen to 168 per minute, and the deflections were reduced as shown, but within six seconds of the termination of the attack the character of the deflections recovered and the rate was restored to 250 per minute. At the end of the attack registered in gram 16 the flutter rate recovered from 165 per minute to 214 per minute in 4 seconds, but further progress could not be followed as the gram ends.

As with the normal mechanism, so also in flutter, recovery of the previous character may be affected by a single isolated contraction of the ventricle. For instance, in gram 15 (see Fig. 7) after 36.2 seconds of ventricular silence, a single contraction occurred, followed by a further period of silence of at least 8 seconds' duration. The total duration is unknown because at this point movement of the patient interrupted the gram. Within 5 seconds of this single ventricular contraction, however, the flutter rate had recovered from 187 per minute to 230 per minute, the extent of deflection improving with the rate.

CONCLUSIONS.

The records obtained in this case show that the auricles were profoundly affected during prolonged periods of ventricular inactivity, and their reaction to the total cessation of circulation may be summed up as follows:—

After a brief preliminary period of quickening the auricles begin to give evidence of exhaustion by a steady diminution of rate, with this there is a decrease in amplitude of deflection. Sooner or later the normal contractions cease, their place being taken by irregular contractions, or attempts at contraction, emanating from various foci. These are interspersed between attempts to establish a regular but slow rhythm, the stimuli for which may arise at the normal site, or near it, or from some frankly ectopic focus.

Finally, there may be periods during which the auricle is completely silent, lying idle and not attempting to contract. On the resumption of ventricular activity, however, even though it be a single isolated beat, there is a conspicuous and rapid recovery on the part of the auricle. Finally, even when the auricles were in a state of flutter, similar tendencies were seen. The flutter mechanism was not abolished but it appeared to be progressively depressed, and, like the normal mechanism, showed rapid restoration as the immediate result of the resumption of ventricular activity.

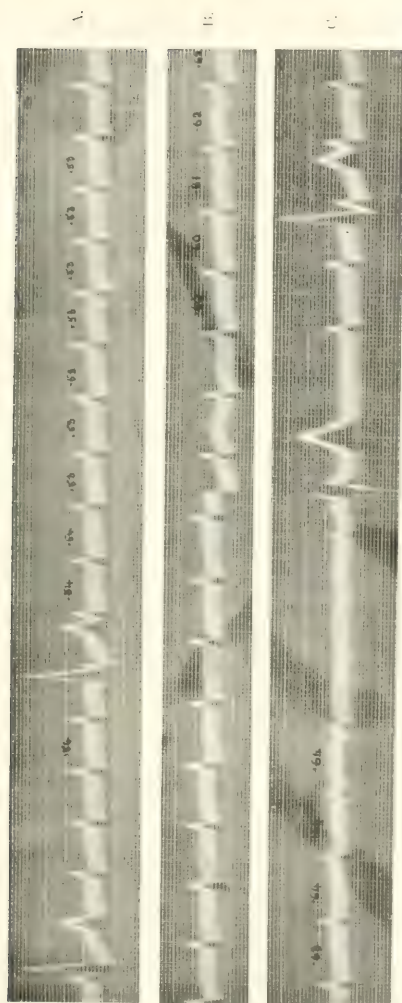


Fig. 1. (Giam 2. Table 1.) Slowing of auricle leading up to failure, and recovery at end of attack. A. The beginning of the attack. Auricular action is of normal type, but there is quickening. Average rate 113 per minute. B. 31st-38th seconds of same attack. The auricle is slowing. Average rate just under 100 per minute. C. Direct continuation from B, showing end of attack. The auricle slows still more, to 91 per minute, and there is progressive decrease in the amplitude of the deflection. The attack lasted 16 seconds. The ventricular beat which ends the attack, rapidly followed by recovery of the auricle.



Fig. 2. (Gram 8. Table 1.) Irregular action of auricle after failure of normal mechanism. Shows the 25th to 33rd seconds of the attack. The auricle had failed at the 17th second. In addition to two pairs of auricular ectopic beats, and one which may have arisen near the sino-auricular node, there are various slight irregular oscillations of the string which may have been due to auricular activity.



Fig. 3. (Gram 17. Table 1.) Slow ectopic rhythm of auricle after failure of normal mechanism. Shows 17th to 26th seconds of the attack. The normal auricular mechanism had failed abruptly at the 15th second. Two beats giving low deflections of normal upright direction are followed by a series of ectopic beats.



Fig. 4. (Gram 3. Table 1.) Auricular silence at end of attack, and recovery following a single ventricular contraction. The ventricle has been silent for 63.5 seconds before the single contraction seen, and there had been no evidence of auricular activity during the last 13 seconds of the attack. For the first 3 seconds after the ventricular beat the whole heart is silent. Then two ectopic auricular contractions occur, and after these the normal auricular mechanism reasserts itself, starting at a slow rate but quickening. A second ventricular contraction occurred at the 74th second.

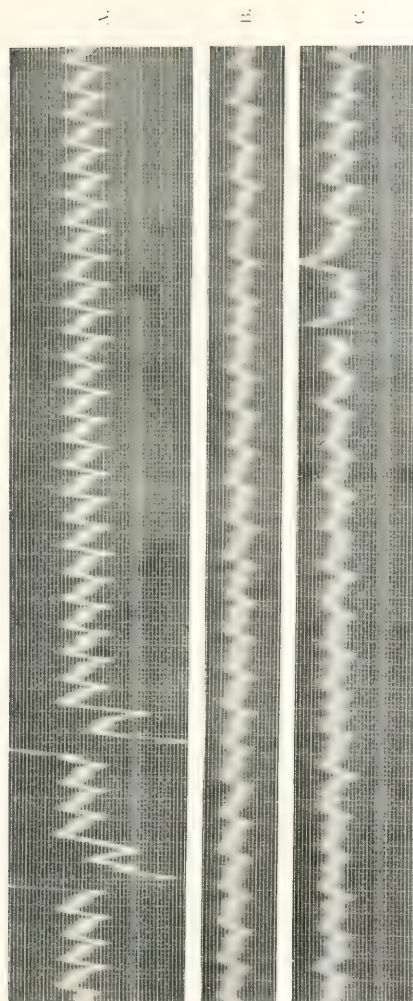


FIG. 5. (From 16, Table I.) Auricular flutter. Reduction in rate and extent of deflection during an attack. A. The beginning of the attack. The flutter rate is 240 per minute. B. The middle (29th-36th seconds) of the same attack. The flutter rate has fallen to 180 per minute, and the deflections are much reduced in amplitude. C. The end of the same attack. The attack lasted 61 seconds. The flutter rate has fallen to 165 per minute, and the reduced deflections show some slight irregularity.



Fig. 6. (End of attack before gram 16; Table I.) Recovery of flutter rate and character on resumption of ventricular beat. The end of an attack the beginning of which was not registered. Flutter rate at end of attack 168 per minute, and deflection low. First ventricular beat is immediately followed by increase in rate and extent of deflection. Within 6 seconds the rate had increased to 250 per minute.

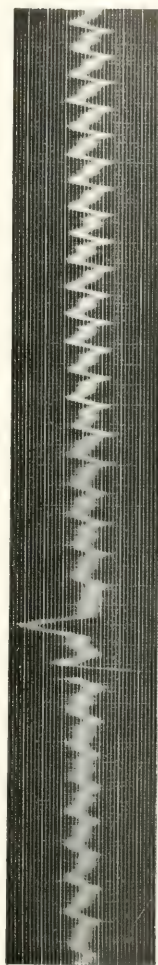


Fig. 7. (Gram 15; Table I.) Recovery of flutter rate and character resulting from a single ventricular contraction. The single ventricular beat seen ended an attack of 36 seconds duration. During the attack the flutter rate had slowed from 250 per minute to 180 per minute, and the amplitude of deflection had been reduced as seen. Within 5 seconds of the ventricular contraction the rate had increased to 230 per minute, and the deflections had increased in amplitude.

NOTES ON THE EFFECTS OF QUINIDINE UPON PAROXYSMS OF TACHYCARDIA.*

By C. C. ILIESCU and A. SEBASTIANI.

(*Cardiac Department, University College Hospital Medical School.*)

SINGER AND WINTERBERG¹, in a recent paper, report a series of nine cases of paroxysmal tachycardia, including one case of ventricular tachycardia and eight of auricular tachycardia. Long paroxysms of rapid heart action in these patients were treated with single doses of quinine bihydrochloride given intravenously.† The doses used were 0.4, 0.5 and 0.75 of a gramme, the most usual dose being 0.5 of a gramme. In six of the reported cases the paroxysmal attack was brought to an end by this treatment within a few seconds or at the most ten minutes after the injection. Four cases in which the paroxysmal attack was stopped showed a slowing in the heart rate before the resumption of the normal mechanism. The rates of heart beat in these four cases, before and after the injection and at the resumption of the normal heart rhythm, were :—

Case.	Before.	After.	Fall.
1	249	198	51
2	f 180 176	150 167	30 9
3	180	144	36
4	f 245 230	200 200	45 30

The fall of the rate thus varied between 9 and 51 beats per minute. Of the other two cases successfully treated, the one manifested a preliminary rise of heart rate of 30 beats per minute, the other presented no change of rate until the normal rhythm was resumed abruptly. In the three cases unsuccessfully treated no change of heart rate was noticed.

* Observations undertaken on behalf of the Medical Research Council.

† Only one case was treated, and this case unsuccessfully, by means of quinidine given by the mouth.

Parkinson and Nicholl² treated six cases of paroxysmal tachycardia, comprised by one case of ventricular tachycardia and five of auricular tachycardia with quinidine given by the mouth, the doses varying from 5 to 40 grains per day, and found that in four cases the incidence of the attacks was uninfluenced, and in two cases their frequency was diminished, but only for three days. Scott³ has noticed, in repeated observations, in a case of short and repeated attacks of paroxysmal tachycardia of ventricular origin, that a single dose of 0.4 of a gramme of quinidine administered by the mouth invariably freed the heart from paroxysmal attacks within 30 to 60 minutes of the dose's administration. A dose of 0.6 of a gramme of quinidine, reduced subsequently to 0.2 daily, kept the patient free of the attacks for a period of six months: the drug being stopped, the disturbances reappeared and a new daily treatment of quinidine again abolished the attacks, clearly showing the control which quinidine had upon the tachycardia. Scott noticed that under the influence of quinidine the first beats of the paroxysm were less premature than in the uninfluenced heart.

We have had under our observation two cases of paroxysmal tachycardia, both of which were of auricular origin. The first case was that of a woman of 35 years, who had attacks of auricular tachycardia lasting from 12 to 24 hours at intervals of 2 or 3 weeks. The first attack, experienced after admission to hospital, was stopped by pressure on the right vagus. Two weeks later she had another attack, which began at 1 p.m. At 3.40 p.m. a single dose of 0.4 of a gramme of quinidine was administered by the mouth. At 20 minute intervals electrocardiographic records were taken until 6.35 p.m., and no material modification of the heart rate was noticed, the rate varying between 164 to 170 beats per minute. At midnight, during the stage of recovery from quinidine, the attack ended.

The second case observed manifested what is evidently a somewhat unusual behaviour towards quinidine. The patient, a man of 24 years, came to the out-patient department on October the 30th, complaining of palpitation and giddiness experienced during rest and exercise, which prevented him from carrying on his usual occupation of engineer and from resting at night. These symptoms had been present for nearly three years, and treatment at various hospitals had given him no relief. The electrocardiogram taken on the first day of observation showed short attacks of 6 to 8 beats of paroxysmal tachycardia of auricular origin, each followed by a long post-paroxysmal pause. A single normal beat followed and was at once followed by a further paroxysm. The rate of the heart in these paroxysms was 164 beats per minute.

Admitted to hospital on November the 1st, he presented an identical disorder of the heart beat. After preliminary doses of 0.2 and 0.4 of a gramme of quinidine the patient was re-examined on the 8th of November. After lying at rest for three-quarters of an hour, two electrocardiograms (lead II) were taken at 30 minute intervals. These two records were exactly similar to the first record taken on October the 30th, and showed short attacks of

tachycardia of 4 to 11 beats, each followed by a long post-paroxysmal pause and a single normal beat. At 11.55 a.m., a single dose of 0.5 of a gramme of quinidine* was administered and electrocardiograms were taken until 1.30 p.m. Half-an-hour after the administration of the drug it was noticed that the paroxysms tended to become longer and their rate to decrease. At 1.10 p.m. the attack of tachycardia exceeded 42 beats, and the rate, which before the quinidine administration was 193, had fallen to 103 beats per minute, thus showing a decline of 90 beats per minute. At 1.20 p.m. the attacks began to shorten and in the pauses between them 1, 2 or even 3 normal beats appeared; the rate still continued to decline, however, and reached 92 beats per minute. At 1.30 the rate was 87 beats per minute and the electrocardiographic records were stopped before a continuous normal rhythm was resumed (Table I).

On November the 15th the patient was again investigated, having had no quinidine in the interval. On this occasion 0.6 of a gramme of quinidine was given. Table II shows the events of Table I to be repeated. The attacks of tachycardia, which before the administration of the drug were of from 2 to 9 beats, lengthened until 80 minutes after the taking of the drug a continuous tachycardia became established which lasted 20 minutes. At 4.55 p.m., 128 minutes after the drug was given, the normal rhythm was resumed (Fig. 3. B). Hand in hand with the lengthening of the paroxysmal attacks, a progressive decrease in their rate was noticed; the initial rate was in the average 180 beats per minute; by 4.35 (Fig. 3. A) it had dropped to 114 beats per minute, thus showing a fall of 66 beats per minute. The normal rhythm was resumed at a rate of 82 beats per minute and was maintained with very small variations of rate for 95 minutes; during the first 20 minutes it was interrupted by occasional extrasystoles arising from the same source as the paroxysms. On the next day the usual mechanism of short rapid paroxysms had returned.

On December the 23rd a single dose of 0.6 of a gramme of quinidine was given at 10.10 a.m.. On this occasion the effect of the drug was a little more delayed than usual. At 10.30 a.m., 20 minutes after the drug was given (Fig. 1, a), the rate (158 beats per minute) and length of the attacks were practically unchanged. At 11.30 (Fig. 1, b), 80 minutes after the administration of quinidine, the rate of the attacks was 157 and their length also remained practically unchanged. Twenty minutes later the effect of the drug was manifested by the lengthening of the attacks and by the fall in rate, which reached 150 beats per minute. At 12.10, 120 minutes after the drug was given (Fig. 1, c), the attacks varied in length from 22 to 26 beats and the rate had fallen to 117. From 12.40 to 12.58 the attack of tachycardia was continuous. The last paroxysmal rate observed was 83 beats per minute; the normal rhythm was resumed at a rate of 79 beats per minute at 1.7 p.m. (Fig. 1, e). In this and the remaining curves the shape of the

* Pure dried base containing no more than 0.5 per cent. impurities.

normal P deflection and the P' deflection of the paroxysm are distinctive, though in records taken at a relatively slow speed, the differences in shape are only clear if the curves are closely examined. They are much easier to see in curves taken upon paper which is travelling faster (as in Fig. 3). In these it is easy to appreciate that the normal P has a sharper upstroke, while the P' wave of the paroxysm and of isolated extrasystoles has a slower upstroke and a double summit. At 1.40 p.m. the normal rhythm was again interrupted by attacks of tachycardia, the rate of which did not exceed 85 beats per minute. Until 4.10 p.m. the paroxysmal rate slowly accelerated; it had then reached a rate of 94 beats per minute. During this time the length of the paroxysms varied from 2 to 30 beats, the paroxysms alternating with 1, 2 or 3 normal beats. At 4.40 p.m. the record started with a long run of 28 normal beats at a rate of 90 beats per minute, followed by a paroxysm exceeding 81 beats, whose rate was 120 to the minute. From 4.40 till 5.32 p.m. there was a slight decrease in the rate of the paroxysm from 120 to 90 beats per minute. Immediately afterwards the rate began rising again, and at 6.35, when the last record was taken, it had reached 115 beats per minute.

The electrocardiogram taken next morning at 10.25 showed short paroxysms of from 6 to 10 beats, at a rate of 162 beats per minute.

The paroxysmal attacks in this patient were unusual in another respect, namely, in their reaction to exercise. If the patient lifted himself by placing his foot on a chair and standing up on the chair 20 to 30 times on each foot, the invariable reaction was a disappearance of the paroxysms. At the end of such exercise the normal rhythm was always seen, its rate averaging 120 beats per minute. It fell in a usual period of 3 to 15 minutes to an average rate of 100 per minute. The first paroxysm then started abruptly at a rate of 175 to 160 per minute. At first the paroxysm would be relatively long, being separated by the usual pause and single normal beat: after a time it would become shorter until the original mechanism was restored. This observation was made repeatedly on a number of occasions.

Discussion.

The most constant effect of pure quinidine administration in cases of auricular fibrillation is to lower the rate of the auricular oscillations. This effect appears to be invariable, provided that the dose of alkaloid is adequate. Similar effects are noted with commercial preparations of quinine. In so far as observations have been made upon auricular flutter, a similar, though less intense, action has been seen. This slowing of rate in auricular fibrillation and flutter has been explained on the basis of the theory that these two disorders of the heart beat are due to simple forms of circus movement in the auricle, and the explanation appears in these instances to be adequate. It is now clear that cinchona alkaloids are capable of slowing a heart which is affected by what has been termed simple paroxysmal tachycardia. The action cannot as yet be stated to be constant, as it failed to appear in two

of Singer and Winterberg's cases and in the first case here recorded. It is possible that the reaction would be constant, providing the doses of the drug used were increased. In this connection it is to be pointed out that when a test dose of quinidine is given in cases of flutter, the slowing produced is far less than that yielded by an equal dose given to a case of fibrillation. It may be that the usual effect of cinchona alkaloids upon paroxysmal tachycardia differs only quantitatively from that produced upon fibrillation and flutter, and that the degree of fall is governed by the original rate of auricular beating. The preliminary slowing of paroxysmal tachycardia and subsequent and abrupt transition to normal rhythm observed in most of Singer and Winterberg's cases, suggests, though it by no means proves, that paroxysmal tachycardia may depend essentially upon circus movement, as do flutter and fibrillation.

TABLE I.

Time.	Paroxysms of :	Rate.
11.0	5 to 9 beats	193
11.30	4 to 11 beats	194
11.55	Quinidine 0.5 of a gramme	
12.25	7 to 14 beats	180
12.45	18 to 24 beats	170
1.0	Over 58 beats	140
1.10	Over 42 beats	103
1.20	7 to 9 beats, followed by 1, 2, or 3 normal beats	92
1.30	7 beats, followed by 1 or 2 normal beats	87

TABLE II.

Time.	Paroxysms of :	Rate.
2.10	6 to 8 beats	181
2.15	6 to 10 beats	180
2.30	4 to 9 beats	181
2.40	4 to 9 beats	180
2.45	2 to 9 beats	179
2.47	Quinidine 0.6 of a gramme	
3.30	8 to 17 beats	164
3.50	45 to 62 beats	142
4.5	Over 100 beats	140
4.10	Continuous tachycardia	132
4.15		130
4.20		123
4.25		124
4.30		114
4.35	Normal rhythm, interrupted by isolated extrasystoles	114
4.55		82
5.0	Normal rhythm, interrupted by isolated extrasystoles	77
5.35	Normal rhythm	78
6.0	Normal rhythm	82
6.30	Normal rhythm	81

TABLE III.

Time.	Paroxysms of :	Rate.
9.30	2 to 5 beats	164
9.40	2 to 7 beats	160
9.50	2 to 6 beats	163
10.0	2 to 3 beats	166
10.5	2 to 6 beats	161
10.10	Quinine 0.6 of a gramme	
10.30	2 to 7 beats	158
10.50	3 to 8 beats	159
11.10	2 to 7 beats	159
11.30	4 to 7 beats	157
11.50	3 to 10 beats	150
12.0	3 to 10 beats	142
12.10	22 to 26 beats	117
12.15	Over 29 beats	115
12.20	Over 40 beats	112
12.25	Over 35 beats	112
12.30	Over 40 beats	108
12.35	Over 40 beats	99
12.40	Over 116 beats	94
12.45	} Continuous tachycardia {	94
12.48		90
12.50		88
12.55		85
12.58	Over 60 beats, followed by one or two normal beats	83
1.7	<i>Normal rhythm, interrupted by isolated extrasystoles</i>	79
1.40	Over 20 beats	85
2.10	Over 30 beats	82
2.40	10 beats	82
3.10	7 to 21 beats, followed by one or two normal beats	90
3.40	7 to 30 beats, followed by one or two normal beats	90
4.10	10 to 27 beats, followed by one or two normal beats	94
4.40	28 normal beats, followed by 81 paroxysmal beats	120
4.48	Over 15 beats	100
4.58	3 to 15 beats	100
5.7	Over 40 beats	90
5.32	Over 43 beats	90
5.50	Over 45 beats	105
6.10	Over 29 beats	110
6.35	2 to 50 beats, followed by 2, 3, or 4 normal beats	115
10.25 a.m. next day	6 to 10 beats, followed by 2, 3, or 4 normal beats	162

The case which is recorded in detail in this article differs from those previously recorded in that the slowing of rate is continuous and progressive until a rate closely approaching the potential rate of the sino-auricular node is reached. Then the normal rhythm is resumed and continues until, as the effects of the drug wear off, the abnormal beating reasserts itself. It appears to us to be most improbable that the paroxysm of tachycardia in this patient was dependent upon circus movement; the length of the slowest paroxysmal cycles, namely, 0.72 of a second, seems to place such an explanation altogether out of court. But if this profound slowing to the rate of the normal rhythm in the same case places circus movement out of court, it does so for this particular patient and not for cases of paroxysmal tachycardia generally. The fact that in most such cases the transition from paroxysmal to normal rhythm is abrupt, and accompanied by an instant and profound fall of rate, may indicate that the tachycardia in our own case, in which different phenomena are witnessed, is of an unusual and distinct type. A distinction also seems to be indicated by the unusual reaction of the mechanism to exercise.

In regard to further possible explanations of why cinchona alkaloids are capable of terminating paroxysmal tachycardia, we have no suggestions to add to those offered by Scott,³ and agree with him that until further data are collected, such discussion must remain hypothetical. His chief suggestion was that quinidine, by lengthening the refractory period of the ventricle, renders the appearance of early premature beats impossible in this chamber, and that the abolition of tachycardia is dependent upon a similar influence. His reason for hesitating to conclude definitely that quinidine lengthens the refractory period of the ventricle—he was dealing with ventricular paroxysms—has since been removed by the direct observations of Drury¹ and his collaborators.

Summary.

An instance of frequent short paroxysms of tachycardia is recorded in which single doses of quinidine exerted the following constant effects. The rate of beating was reduced, while the paroxysms became of longer duration and eventually continuous; the fall of rate proceeded until the paroxysmal rate approached closely to that of the normal rhythm in the same heart; the normal rhythm was then resumed. During the escape of the heart from the influence of quinidine the events occurred in the reverse order.

The disordered mechanism manifested an unusual reaction to exercise, the latter producing an invariable, though temporary, return to the normal rhythm.

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THE VELOCITY OF THE PULSE WAVE IN MAN IN RELATION
TO AGE AS MEASURED BY THE HOT-WIRE
SPHYGMOGRAPH.

By J. CRIGHTON BRAMWELL,* A. V. HILL and B. A. McSWINEY.

(From the Physiological Laboratory and the Royal Infirmary, Manchester.)

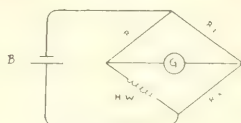
I. Instruments.

A HOT-WIRE as a sensitive detector of air movement has been employed for some years, preliminary experiments on the use of a platinum wire heated by an electric current, for the measurement of wind velocity, having been made by G. A. Shakespeare in 1902. A full account of the employment of a "hot-wire anemometer" has been given by L. V. King⁸ and ⁹. In 1915 P. de Lange¹⁰ described a "Thermophone," an instrument consisting of 24 fine platinum wires kept in a confined space, which, on being heated by the current from a microphone, caused the contained air to expand in time with sound waves reaching the microphone, and so acted as a receiver. In 1916 Tucker patented the converse of this instrument, viz., the hot-wire microphone, which was used for gun-sound-ranging during the war, and remained secret until the publication of an account of it in 1921¹². A preliminary description has been given by one of us⁶ and ⁷, of the use of a hot-wire sphygmograph, and Heald and Tucker⁵ have described experiments in which the hot-wire microphone has been used to record the "body rebound" caused by the heart beat.

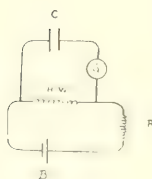
(a) *Method employed.* If a fine platinum wire (11 micron wire obtainable from Messrs. Johnson and Matthey) be connected by copper leads to a battery, and the current adjusted to make the wire red-hot, then on blowing on it, it will be seen to flicker like a match in the wind. The relatively enormous surface (3,600 sq. cm. per c.c. of metal) enables cooling to go on very rapidly, and even small puffs of air cause a considerable fall of temperature in the wire. Such cooling produces changes of electrical

* Working for the Medical Research Council.

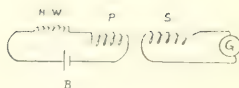
resistance, which can be recorded by means of a rapidly moving galvanometer. Three ways of doing so are shown in Fig. 1. In (1) the method is that of the Wheatstone bridge, the balance being upset by the cooling of the wire and consequently a current running in the galvanometer. In (2) a condenser (10 to 40 microfarads) is put in series with the galvanometer. The variations in the resistance of the hot wire produce variations in the



(1)



(2)



(3)

Fig. 1. Diagrams to illustrate different ways in which hot wire may be employed. B = battery; G = string galvanometer; H.W. = hot wire; C = condenser; R, R_1 , etc. = resistances; P = primary; S = secondary of transformer.

E.M.F. between its ends, and so cause currents to flow in the galvanometer. In (3) the fluctuations of the current in the primary, due to changes of resistance of the hot wire, induce in the secondary of the transformer currents, which are recorded on the galvanometer. In the experiments described in this paper we have uniformly adopted the Wheatstone bridge method, as being more suitable to the relatively slow fluctuations occurring

in the pulse, and as giving more accurate quantitative results. For many purposes, however, the simpler methods (2) and (3) are adequate.

By placing a suitable receiver, either a funnel, a hollow rubber bandage, or a tambour, over an artery, and connecting the receiver to a tube, pulsations of the air, in time with the pulsations of the vessel, will be caused in the tube. Such pulsations will be propagated along the tube with the velocity of sound, say 280 metres per second,* at 15°C. If, now, a suitable carrier, containing a hot wire, be placed in the tube, the pulsations of the air will be recorded on the galvanometer.

(b) *The hot wire.* The first instrument of the kind which we employed was constructed by the Cambridge and Paul Instrument Company. It contained 10 micron copper wire, which was apt to burn out, and owing to the construction of the instrument was difficult to replace. It has, therefore, been redesigned, and the present pattern (Fig. 2) is simple in

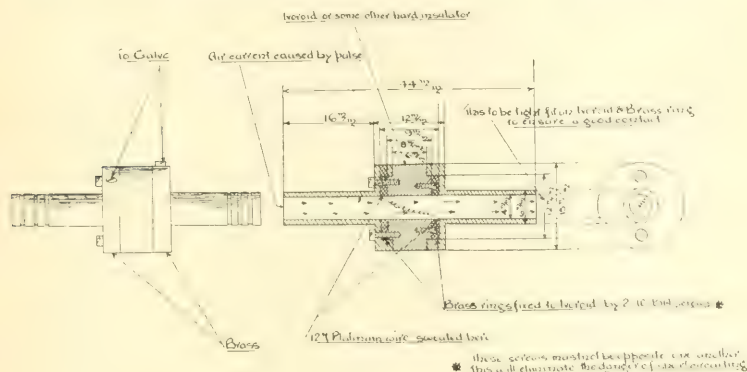


Fig. 2. Hot wire container.

construction, and allows the wire to be replaced easily if it burns out. As a matter of fact this rarely happens. Its design is largely due to Mr. A. C. Downing, of the Physiological Laboratory. We have found 11 micron platinum the most satisfactory wire to use, a little spiral of about 30 ohms resistance passing through a hole in the vulcanite, and being soldered to the two brass rings at the ends. We have tried a variety of other wires, platinum of different diameters, copper and silver. The last two are apt to burn out, and appear to give less sharply defined records than does

* The velocity of sound in a narrow pipe is appreciably less than in the open air. See below.

platinum. Thicker platinum will respond more slowly, thinner platinum (7 micron) will respond slightly more rapidly; no real advantage is gained, however, by using thinner wire, since the 11 micron wire seems to react quickly enough for all purposes, and wire thinner than 11 micron is difficult to manipulate.

(c) *Galvanometer and bridge.* The galvanometer was the ordinary electrocardiograph outfit of the Cambridge and Paul Instrument Company, using a plate, or a paper, camera. We have usually employed a metal (12 micron copper) string in the galvanometer, which, having a low resistance, is more suitable for use with a low resistance circuit: it gives sharper records, and is also more easy to mend if broken. Glass strings, however, give satisfactory results. In most of our observations the "eyepiece" was not used: this diminishes the magnification to about 75 diameters, and so reduces the sensitivity. Ample sensitivity, however, is available, and without the eyepiece more light and neater records are obtained. In most cases the deflections are so large that the string can be used very tight. A string with a complete period of 0.003 of a second is more than sufficiently sensitive.

We have employed also the small Salomonson string galvanometer, manufactured by the Cambridge and Paul Instrument Company. This instrument has two copper strings, and can be used with a small pointolite lamp or arc: it is easily transportable, much cheaper, and appreciably simpler than the ordinary string galvanometer outfit: it has ample sensitivity and a sufficiently short period for most purposes. If required it can be used in conjunction with the ordinary electrocardiograph, so that an electrocardiogram and two hot-wire records can be obtained on the same plate.

On open circuit the motion of the string is imperfectly damped; when a circuit carrying a current through it is opened, a prolonged vibration is set up. When short-circuited through a resistance, the damping of the string is greater the smaller the resistance. The resistance between the galvanometer terminals of the bridge is usually about 30 ohms, and with this the vibrations of the strings are about critically damped. The matter of natural period and damping is an important one, for if it be desired to record with quickness and certainty the rapid series of mechanical events happening in the pulse, it is necessary to employ a recording instrument of short period and preferably just damped. The galvanometer, as employed, having a natural period of about 0.003 of a second, is capable of following very rapid changes without contamination with its own mechanical vibrations, and since it is incapable when sufficiently damped, of showing its own vibrations at all, any oscillations which appear on the record must be due to some external cause, and not to the mechanical properties of the recording instrument. In this respect it has an advantage over other methods of recording the pulse.

The Wheatstone bridge employed was a special one made by Messrs. W. G. Pye, of Cambridge. A dial resistance is provided for the battery circuit, to enable adjustments of the current through the platinum wire to be made. Sufficient current is employed to heat the wire to a temperature just below red heat. A dial resistance is provided in series with, and a dial shunt for, the galvanometer. A spiral ratio resistance (with scales) forms two arms of the bridge, a dial resistance the third arm, and the hot wire the fourth. The resistance of the third arm is usually made about equal to that of the hot wire. Due precautions must be taken in connecting up, in getting the balance, and in manipulating the bridge, in order to avoid breaking the galvanometer string. Three to six accumulators are required.

(d) *Connecting pipes.* The pipe conveying the pulsations from the artery to the hot wire should be as short as possible, for the following reason. A pipe of length l , closed at one end, acts as an organ pipe, and resonates with a frequency of $a/4l$, where a is the velocity of sound. The air, therefore, in a pipe two metres in length has a natural frequency of oscillation of 42* per second, in a pipe one metre long a frequency of 85 per second. Hence, if we wish to avoid contamination of our records with vibration of the air in the pipe, it is necessary to use short pipes.

A set of records was made by gently tapping, and so setting up vibrations in the air inside, a series of rubber pipes of different lengths. The pipes consisted of pressure tubing and were 3.47, 2.54, and 1.74 metres long respectively. The hot wire was near the open end of the pipe, and the other end was closed. The fundamental frequencies† of these pipes should be 24.5, 33.5 and 49.0 per second respectively. We found by measurement that the record showed vibrations at rather less than double these rates, viz., at 41, 54 and 82 respectively. These frequencies are exactly in the inverse ratios of the length of the pipes, as they should be. The hot wire we should expect to respond *twice* to each complete oscillation of the air, once as the air goes in, once as it goes out. The reason why the frequencies observed are not exactly double the calculated ones is the narrow gauge of the pipe employed (about 4 mm.). It is known that the velocity of sound in a narrow pipe is less than in a wide one, and in the pipes employed it would appear to be about 280 metres per second. Thus, in employing a narrow rubber pipe of length 1 metre, with one end open, for recording the pulse, we have to expect vibrations of the air of frequency about 70 l per second. Such artificial vibrations might be expected to interfere with, and to distort, the record of the vibrations of the arteries, which are often themselves fairly rapid. In the case of an instrument like the polygraph, where the transmitting pipe is closed at both ends, the wave-

* Assuming the velocity of sound to be 340 metres per second, as in the open air.

† Calculated from the expression $a/4l$, and assuming a , the velocity of sound, to be 340 metres per second.

length of the vibration is $2l$ and not $4l$, so that the frequency of oscillation of the air in such a narrow rubber pipe is about $140/l$. If l be kept small, the natural frequency of the vibration of the air remains so high that oscillation is unlikely to be excited by the relatively slow mechanical changes occurring in the artery. If, however, l were too great, *e.g.*, several metres, there might be a noticeable interference with the record.

(c) *Receivers.* The receivers placed upon the body and connected to the rubber pipe have been:— (a) for the carotid and jugular, a small funnel of $2\frac{1}{2}$ cm. diameter, or a shallow metal cup as provided with the usual polygraph outfit; (b) for the apex beat, the same, a larger funnel, or a button tambour; and (c) for a limb, a hollow rubber bandage similar to that employed with a sphygmomanometer, strapped round the limb and blown up to a pressure of about 80-100 mm. of Hg.

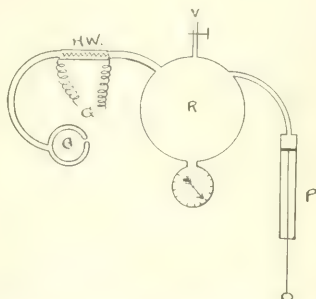


Fig. 3. Arrangement of apparatus for radial syzygmograms. H.W. hot wire; A—armlet; R=reservoir of oscillometer; P=pump; V=escape valve; G=leads to galvanometer.

For the radial pulse we have employed occasionally a spring sphygmograph as supplied with clinical polygraph outfits, but this is apt to develop natural oscillations of its own, and is difficult to adjust with sufficient accuracy to secure the maximal excursion. Since we have worked with large numbers of subjects it has been necessary to employ some simple ready method of fixing a receiver, without delay in adjustment. We have adopted, therefore, the plethysmographic bandage for general use, except in the case of the carotid and jugular pulses and the apex beat. Actually we have used the bandage, pump and manometer of the Pachon "Oscillomètre Sphygmométrique" (Boullite), placing the hot wire instrument fairly close to the bandage, in the course of the pipe running to the reservoir of the oscillometer (Fig. 3). Any simple arrangement, however, consisting of a reservoir, a pump, a pressure gauge, and a bandage will give satisfactory results.

The bandage can be blown up to any desired pressure and read by its own manometer. The oscillogram can conveniently be used to ascertain the maximal excursion, and provides an adequate reservoir for air to flow past the hot wire. It is necessary that the whole system should be airtight, otherwise, in addition to the objection of changing pressure, air will flow past the hot wire throughout the experiment and disturb the records. The hot wire carrier can be rendered air-tight by soaking it in molten paraffin wax. It is necessary also to avoid altering the pressure without first shunting the galvanometer, otherwise a very extensive cooling of the wire may damage the galvanometer string. We have occasionally employed a glycerine tambour: this, however, although easy to fix and use, appears to damp the movement, and, by rounding off the sharp deflections, interferes with accuracy in timing. With all but the bandage receivers the hot wire instrument is simply fixed in the end of the rubber pipe, and left with its other end open. With bandage receivers, however, the inside of the instrument is under pressure, and it is necessary to provide a small reservoir beyond the hot wire to allow air to pass it. A closed bottle, or the reservoir of the oscillogram, connected by a short rubber pipe to the hot-wire instrument, is sufficient.

(f) *Measurement of records.* The records have been measured in three ways: (a) by the use of the Lucas comparator (this method is laborious and unnecessarily accurate); (b) by throwing the image of the record on a screen of squared paper, by means of an enlarging lantern, and adjusting the distance of the screen so that the interval between successive time marks, *e.g.*, 0.2 of a second, occupies an exact distance on the screen, *e.g.*, 20 cm. (by this method, which gives results closely agreeing with those obtained with the Lucas comparator, the intervals can be read off directly in seconds on the screen); and (c) when using prints or records on bromide paper, by the employment of a glass rule etched in millimetres, laid, etched side downwards, directly on the record, and read, if necessary, with a lens (in this way distances can be read to 0.1 mm. with very little trouble, and times, in records going 100 mm. per second, to 0.001 of a second).

II. Interpretation of records.

(a) *Physical considerations.* Owing to the physical principles involved the records obtained with the hot wire differ in form from those given by other sphygmographs. In the first place, since cooling of the wire may be produced by a current of air passing through the tube (Fig. 2) in either direction, both expansion and contraction of the vessel under the receiver give rise to similar deflections in the hot wire record. Secondly, heat is being liberated continuously in the wire by the current passing in it. This heat is being dispersed by conduction, convection and radiation. The temperature of the wire, therefore, remains high and constant until a sudden passage of air cools it. When the passage of air has ceased, the wire rapidly

warms again. The resulting record is comparable with that obtained from a tambour, in which the membrane is perforated by a hole sufficiently large to allow the internal pressure to return to atmospheric at such times as rapid alterations of pressure are in abeyance (Fig. 5). Unless these facts be borne in mind, the records obtained are difficult to interpret. For example, the plateau of sustained pressure, which appears on an ordinary cardiogram of the apex beat, is replaced, in the hot wire record, by two rapid deflections with sharp peaks (Fig. 6). These peaks correspond respectively to the rise of pressure immediately preceding the commencement, and to the fall of pressure following the termination of the plateau, whereas during the plateau itself, the heating of the wire being unopposed, the galvanometer returns to the zero position. Conversely, the plateau form of curve is hardly ever met with in hot-wire records, since it could only be produced by a uniform and continuous alteration of pressure causing constant cooling of the wire, in excess of that due to conduction, convection and radiation when at rest. It will be obvious, therefore, that rapid deflections with sharp peaks can be produced only by sudden alterations in pressure.

(b) *Normal carotid records.* In the case of normal carotid records there are two periods during which the conditions leading to sharp peaks are satisfied, the first when the pressure rises rapidly at the commencement of the carotid cycle, and the second when the pressure falls rapidly during a short period immediately preceding the diastolic wave, that is, during the earliest stage of ventricular relaxation, prior to the closure of the aortic valves. For convenience we have designated the corresponding deflections in the hot-wire record α and β .

In interpreting the *meaning* of deflections observed in records made with the hot wire, it is an advantage to have a synchronous sphygmogram of the more familiar type. This may be obtained by placing in series with the hot wire a small light tambour the movements of which are optically recorded. For this purpose we have employed a Frank segment capsule, but in our earlier experiments obtained quite satisfactory results by using a small tambour about 2 cm. in diameter covered with thin rubber and tightly strung to give it a short natural period (less than 0.01 of a second) with a very light mirror placed near its edge. A beam of light from a pointolite lamp was reflected from the mirror, and focussed on the plate of the camera, care being taken that the shadow of the galvanometer string, and the spot of light from the mirror, came exactly on the same horizontal line on the plate, to ensure simultaneity of the records. By throwing the optical condenser of the galvanometer lamp slightly out of focus the relative intensity of the beam of light from the mirror, and of the general illumination from the optical system of the galvanometer, may be adjusted to produce satisfactory contrast. Since the hot wire responds, not to alterations in pressure but only to air movement, its readings are abolished when the instrument is placed in the course of a closed pipe. Hence in the combined

optical and hot-wire records, it is necessary to place a small reservoir between the hot wire and the tambour, to enable air to pass the hot wire. Such a reservoir will tend to diminish the amplitude of movement of the optical tambour, but by suitable adjustments of the volume of the air space it is possible to vary the relative sensitivity of the two recording instruments, and to obtain a result which will give satisfactory records from both. By fitting the air reservoir with a syphon arrangement, the air-volume can be varied at will until the most satisfactory value is ascertained. A three-way tap connecting the hot wire and tambour enables the reservoir to be cut out entirely, if for any purpose it be desired, by using the optical recorder alone, to obtain the maximal excursion of the latter. It is convenient to fit the reservoir with an outlet tube clamped by means of a pinch cock, in order that the optical record may be brought back to its zero position when the desired pressure has been applied to the carotid receiver. Such an arrangement obviates the necessity for altering the position of the optical tambour when variations in the internal pressure of the system are produced by the application of the receiver. In Fig. 7 the lower curve (black) is a hot wire tracing, and the upper (white) is a simultaneous record, made by optical registration.

The comparison of the hot wire with the tambour records shows :—

- (a) That the deflection α commences at precisely the same moment as the initial rise in the curve of the optical sphygmogram ;
- (b) That the hot wire returns to its zero position while the pressure is maintained during systole ;
- (c) That the commencement of the deflection β coincides with the rapid fall of pressure immediately preceding the dicrotic wave ; and
- (d) That, at the same moment as the dicrotic notch occurs on the optical record, the hot-wire record reaches a sharp point, and subsequently returns to its zero.

From this it may be seen that the first wave (α) of the hot-wire records corresponds to the transmitted rise of arterial pressure immediately following the opening of the aortic valves, and the second wave (β) corresponds to the fall of pressure occurring at the commencement of ventricular diastole, its sharp point being due to, and simultaneous with, the closure of the aortic valves.* These facts have been established by a number of simultaneous observations similar to Fig. 7.

* Making due allowance for conduction time of the pulse wave from the aortic orifice to the carotid artery.

In this connection it seemed to be somewhat surprising that the dicrotic wave was not represented in the majority of the hot-wire records. The explanation appears to be that the rise of pressure due to the dicrotic wave is, in most cases, too gradual to produce cooling of the wire. In optical records the dicrotic wave is much less prominent than in sphygmograms taken with Dudgeon's instrument, where the height and steepness of the ascending limb of the wave are considerably exaggerated, by the mechanical rebound of the recording lever when it is suddenly checked in its rapid descent during the earliest phase of diastole. In certain hot-wire records, however, taken from patients exhibiting a markedly dicrotic type of pulse, the deflection β does exhibit a bifurcated peak (Fig. 8), the first summit corresponding in time to the dicrotic notch of the optical curve, the second being a true representation of the dicrotic wave.

Records obtained from the radial pulse (Fig. 9) by the hot-wire present a general similarity to the carotid sphygmograms, but differ from the latter in the fact that the β wave has a rounded, instead of a pointed, summit.

III. The measurement of pulse wave velocity in living subjects.

(a) *Introduction.* By means of the hot wire it is possible to record the time of arrival of the pulse wave at different points in the body, and so to determine the velocity with which it is transmitted. The rapidity of the initial deflection in the hot-wire sphygmogram enables time intervals to be measured with a degree of accuracy, which is rarely, if ever, possible in records obtained by mechanical means, such as have been employed by most observers¹¹ who have previously investigated this problem. In order to determine the velocity of transmission it is necessary to measure the time taken by the pulse wave to travel along a known length of artery.

(b) *Anatomical measurements.* All the observations described in this paper have been made on the upper limb. The reason for selecting the arm in preference to the leg is that the anatomical disposition of the arteries in the former, in the living subject, allows one to arrive at a more accurate estimate of their length than is possible in the latter situation. In the erect posture with the arm extended at right angles to the long axis of the body, the subclavian-axillary-brachial trunk with its direct continuation, the radial artery, may be mapped out by a straight line drawn from the sterno-clavicular joint to a point at the wrist immediately to the inner side of the styloid process of the radius. Similarly with the head thrown slightly backwards, the right common carotid artery, and the commencement of the external carotid, may be marked out on the surface of the body by a straight line drawn from the right sterno-clavicular articulation to a point in the neck immediately below the angle of the jaw, where the pulsation can be felt with the finger. Hence by recording synchronous sphygmograms from the right carotid and right radial pulses, and by measuring the

distances from the right sterno-clavicular joint to the points in the neck and wrist from which the two records are obtained. it is possible, by subtracting the one measurement from the other, to calculate the distance transversed by the pulse wave in the time which elapses between the commencement of the carotid and radial primary deflections.

In a recent paper Bazett and Dreyer¹ maintained that the velocity of the pulse wave is much higher in the smaller than in the larger arteries. We are at present making further observations on this subject, but the values given in the present paper refer only to the mean velocities recorded over the total length of the arteries in the upper limb as defined above. All our observations have been made with the subject sitting at ease in a chair, with his muscles completely relaxed. The carotid pulse may be most easily recorded in this position, as the force of gravity assists in emptying the arteries during diastole, and hence the arrival of the pulse wave produces a greater excursion of the arterial wall.

The total distance on which these calculations are based in the case of an adult is only about 40 to 60 cms. It is important, therefore, that the measurements should be made with care and accuracy, since a difference of 1 cm. in measurement would introduce an error of about 2 per cent.,

It is realised that the innominate artery may not always divide into its two terminal branches immediately behind the sterno-clavicular joint, but since the horizontal extent of this articulation is considerable it appeared advisable to take our measurements in every case from the midpoint of the sternal end of the clavicle. For the sake of convenience the point chosen at the wrist was the tip of the styloid process of the radius, and from this measurement was deducted the width of the bandage employed.

Under certain pathological conditions the limb arteries follow a tortuous course, and in such cases the measurements referred to above will be an underestimate of the actual length of the arteries concerned, the calculated value of pulse wave velocity being less than the true value. This source of error, however, is not likely to affect, to any appreciable extent, the results obtained from young and healthy individuals, especially since the arm is kept extended; and in the case of older subjects, all those in whom tortuosity of the superficial arteries could be detected have been excluded from the group considered in the present paper.

(c) *Receivers.* The carotid pulse is recorded with a cup receiver and the radial with a plethysmographic bandage. The pressure used in the bandage has generally been that which is found to yield the largest oscillations.

As will be seen from the record shown in Fig. 10, the radial upstroke does not occur until the carotid deflection is approaching its base line. Consequently, instead of recording the two pulses on separate strings of the galvanometer, it is possible, by connecting the two hot-wires in parallel to the same bridge, to record their alterations in resistance on the same galvanometer string (Fig. 11).

(d) *Time intervals.* When the latter method is employed, the commencement of the radial upstroke which corresponds to the moment when the second wave suddenly begins appreciably to affect the record, occurs slightly later than when the two pulses are recorded on separate strings, since the rapidity with which the carotid deflection descends tends to neutralise a movement in the opposite direction which is relatively slow in its initial stages. Consequently the velocities calculated from records in which both pulses are recorded on the same galvanometer string have values which are somewhat lower than those in which the pulses have been recorded separately. Since, however, it appears that the difference rarely exceeds 10 per cent., we have included the results obtained by both methods in the present series of observations. In Fig. 4, which shows graphically the results obtained, the observations by the two methods are indiscriminately mixed: on the whole, however, we regard the two-string method as preferable.

The points selected for measurement when both pulses are recorded on the same string are (a) the commencement of the initial deflection as defined below, in the carotid, and (b) the sharp point of the V formed at the junction of the carotid and the radial primary deflections.

It is necessary further to define exactly what is meant by the commencement of the carotid upstroke, as otherwise there is apt to be some discrepancy in the measurements made by different observers. In order to overcome this difficulty, and to obtain uniformity of measurement in different records, we decided to adopt the following convention. The commencement of the carotid deflection is taken as the middle of the recording upstroke where it is cut by the continuation of the immediately preceding base line (Fig. 12). It is realised that this procedure is to some extent arbitrary, but in the last resort there can be no precise beginning to the wave; it *must* rise gradually, so that it is necessary to adopt some convention as to the point from which to measure. The point we have selected is convenient and simple to use, and even if another point were to give results differing from ours by a few thousandths of a second, the fact that we have consistently used the same point makes our readings comparable with one another. This convention has been adhered to throughout. Only those cycles in which the commencement of the upstroke could be defined with certainty were selected for measurement, and since the records were measured to 0.1 mm. the greatest possible error in any particular case would be 0.05 mm. Where, therefore, both the radial and carotid upstrokes were measured, the total possible error in the carotid radial interval in a single cycle would be 0.1 mm., and since each of the results given is the average of three cycles, the "probable" error would be much less than 0.1 mm.. The total length of the carotid radial interval varied in different records (owing partly to variation of the speed at which the paper was moving, and partly to the variation in the actual time intervals recorded in different subjects) between 5 and 10 mm.. Hence

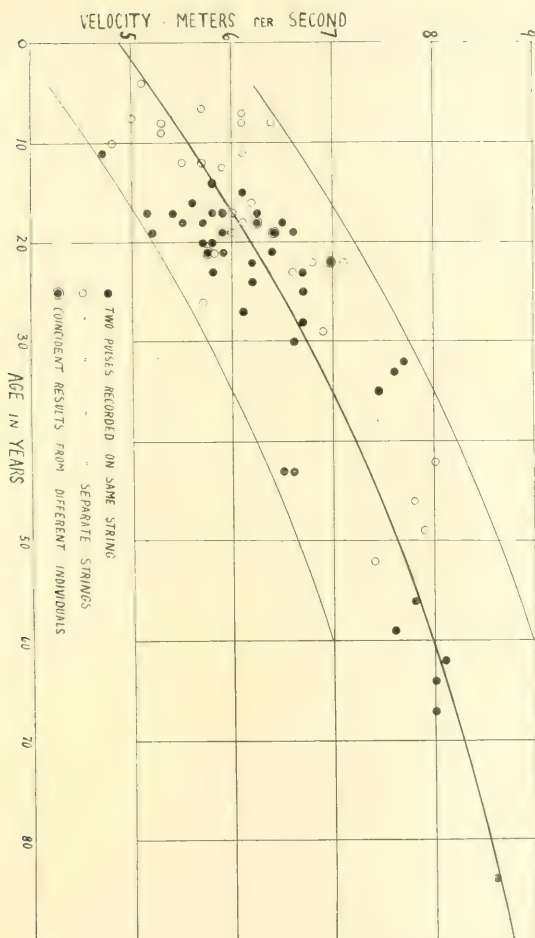


Fig. 4. Diagram of results obtained in 74 experiments. Mean pulse wave velocity in metres per second is plotted (vertically) against age in years (horizontally). Each point represents the mean of three observations. A mean curve is drawn through the observations, and other lines at a distance corresponding to one metre per second above and below the mean curve to indicate the limits of variation.

the "probable" percentage error due to inaccurate measurement would be much less than 1 to 2 per cent. Errors due to variation in the speed of the camera motor are very small, since no cycle was accepted for measurement in which the length of the adjacent time intervals of 0.2 of a second differed by more than 2 per cent..

(e) *Relative sensitivity of recording instruments.* Not infrequently it happens that, in records taken from two different parts of the body, such as the neck and wrist, the amplitude of the deflections are very different, whereas it may be desirable that they should be reduced to roughly the same size. If the two pulses be recorded on separate strings, this may easily be arranged by means either of the shunt or the resistance in the galvanometer circuit, the sensitivity of either string being reduced by the required amount. But in the case where both pulses are recorded on the same string, it is necessary to place a resistance box (0 to 100 ohms) in series with the radial hot wire. It is then possible to vary the relative sensitivity of the two wires, the radial having its sensitivity reduced by the resistance in series with it. Furthermore, if two hot wires of unequal resistance be employed in parallel with the same bridge and string, the wire of higher resistance will have a lower sensitivity. This fact may be of convenience in adjusting the sizes of the two records.

(f) *Radial armlet.* The broad plethysmographic bandage was employed in all our earlier observations. We have used also a narrower bandage, similar in all respects to that previously employed, with the exception that its width was 2.5 instead of 8 cms.. In the case of children this narrow bandage gave satisfactory results; but in adults, in whom the artery was separated from the surface by a considerable amount of subcutaneous tissue, it was found that with such a narrow bandage, in order to obtain excursions of sufficient amplitude, considerably higher pressures had to be employed. This was less comfortable for the subject, and since discomfort might be liable to lead to reflex rise in blood pressure, it was decided in the case of adults to revert to the wider bandage.

(g) *Effect of pressure by the receiver.* Another possible source of error which had to be taken into account, especially when the narrow bandage was employed, was the fact that if a pressure higher than the diastolic were applied by the receiver the upstroke might not occur till the pressure in the artery had risen to the pressure in the bandage. If such an error did exist, it would tend to vary according to the pressure with which the receiver was applied. It was shown, however, by repeated observations on the radial pulse that considerable variations of the pressure in the bandage produced no detectable difference in the results obtained, and the pressure in the bandage has never been much higher than the diastolic.

(h) *Selection of records.* In arriving at our results the method we have adopted has been as follows. Each record comprises from six to ten cycles. Of these, the three in which the deflections appear to be most

sharply defined are selected by eye and measured. If the measurements of any two of the three selected cycles differ from one another by more than 5 per cent., a fourth cycle is measured. Then, if three of the four cycles agree to within 5 per cent., the average of these three is taken, otherwise the whole record is rejected. This procedure was adopted after careful consideration for the following reason. In those cases in which the measurement of a single cycle differed to any appreciable extent from those of its fellows, it was found that the average of all the cycles in the record agreed more closely with the average of the three normal cycles than with the four, including the abnormal cycle in question. Such abnormal cycles are bound to occur from time to time in the course of a long series of observations, and their inclusion in the averages would, we believe, give results which would represent less accurately the values which we are endeavouring to measure.

(j) *Calculation of results.* After the measured carotid-radial interval has been converted into time, it is necessary to make a correction for the difference in length of the tubes connecting the carotid and radial receivers to their respective hot wires. If, for example, the former be 50 cms. long, and the latter only 15 cms. (taking the velocity of sound in these tubes as 280 metres per second) the carotid pulse will be recorded 0.0012 of a second too late as compared with the radial, and the recorded time interval on the plate will, therefore, be too short by that amount.

(k) *Results obtained.* The results of our observations on 74 normal healthy individuals are shown in Fig. 4. A general enquiry into past illnesses and present tolerance for exercise was made in each case, and where there had been any serious illness, only those subjects in whom subsequent athletic achievements appeared to exclude cardio-vascular changes were included in the present group. Owing to the wide variations which occur in pulse wave velocity under pathological conditions³ it appeared necessary to adopt some such standard of normality in selecting subjects for the present investigation.

The ages of the subjects varied from 4 up to 84, and their pulse wave velocities from 4.7 to 8.6 metres per second. In the case of individuals under 25 years of age we have made 53 observations, which number should be sufficient to enable us to obtain a fairly accurate idea of the limits of normal variation. Amongst older subjects, on the other hand, the number of observations is small (21). But the fact that all of those observations which we have made tend to fall in close proximity to the continuation of the curve giving the mean values in younger subjects, suggests that the same general relationship holds good. In Fig. 4 the mean pulse wave velocity is plotted graphically against the age, and a mean curve is drawn through the observations. Further, the maximum deviation from the mean curve appears to be about ± 1 metre per second, and lines are drawn on the figure that distance above and below the mean line. The results obtained

from children under 15 years of age are less uniform than those from young adults. This may, perhaps, be explained by the greater tendency to variation in blood pressure in the former case. As we have shown elsewhere^{7 and 11}, variations in blood pressure play an important part in modifying the elasticity of the arterial wall. In the case of older people a tendency to wider deviation from the mean might have been expected on account of greater variability in the condition of the arterial walls: the number of observations, however, made hitherto at the higher ages is insufficient to enable us to arrive at a definite conclusion on this point.

It is interesting to calculate from the mean curve given in Fig. 4 the actual elasticity of the arteries at different ages. According to Bramwell and Hill² the percentage increase of volume of an artery per mm. increase of pressure is equal to

$$\frac{12.7}{(\text{Velocity of pulse wave})^2}$$

Age	5	10	15	20	30	40	50	60	70	80
Mean velocity	5.2	5.55	5.9	6.2	6.75	7.2	7.6	8.0	8.3	8.55
Mean elasticity	0.47	0.41	0.36	0.33	0.28	0.24	0.22	0.20	0.18	0.17

It is seen that, as age increases, there is a notable decrease in the elasticity of the arteries, at the actual diastolic pressure of the individual, a result which explains the well known fact that the pulse pressure and the systolic pressure are considerably increased with age. The difference between the diastolic pressure of young adults and that of older people is relatively small. If, however, the elasticity (*i.e.*, the mean percentage increase of volume of the artery per mm. increase of pressure) be halved between the ages of 10 and 60, then, for a given relative output of the heart per beat, the pulse pressure will be about doubled and the systolic pressure considerably increased over the same interval of years.

SUMMARY.

The hot-wire sphygmograph consists of a fine spiral of platinum wire heated by a battery. Pulses of air from suitable receivers placed over pulsating points on the surface of the body cool the wire, and produce alterations in its electrical resistance which can be recorded on a string galvanometer. By this means instrumental lag can be reduced to a minimum, contamination of records by mechanical vibrations is avoided, and the time-relations of different cardio-vascular events can be measured with a high

degree of accuracy. The rapidity with which the hot wire sphygmogram leaves its base line increases with the rate of change in pressure in the artery. Normal carotid records show two sharp deflections, the first due to the initial rise of pressure following the opening of the aortic valves, and the second due to the fall of pressure at the commencement of ventricular diastole.

By recording simultaneous hot-wire sphygmograms of the radial and carotid pulses, the velocity of transmission of the pulse wave may be measured with accuracy. A series of 74 such observations, in normal subjects, shows that there is a definite relationship between age and velocity. The mean value rises from 5.2 metres per second at the age of 5, to 8.6 metres per second at the age of 84. So far as these observations go, the greatest deviation from the mean curve for different ages is less than 1 metre per second. During the interval between 10 and 60 years of age the volume elasticity of the arteries is halved. This result explains the increase of pulse pressure and of systolic pressure with age.

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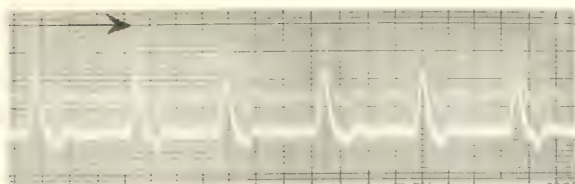


Fig. 5. Radial sphygmogram, recorded by optical method. The recording tambour was perforated by a hole of sufficient size to allow the record to return to its base line when rapid changes of pressure were in abeyance. The initial deflection is very similar to that given by the hot-wire sphygmograph.

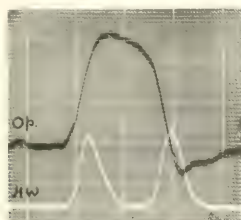


Fig. 6. Synchronous optical (Op.) and hot wire (H.W.) records of apex beat. (Slightly reduced in size.)

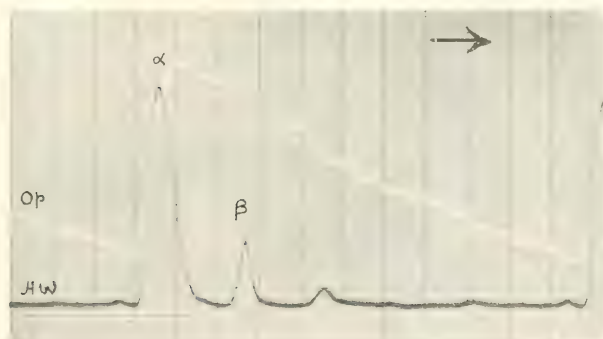


Fig. 7. Synchronous optical (Op.) and hot wire (H.W.) sphygmograms of carotid pulse. α —Primary; β —Secondary deflection. Time intervals 0.1 of a second.

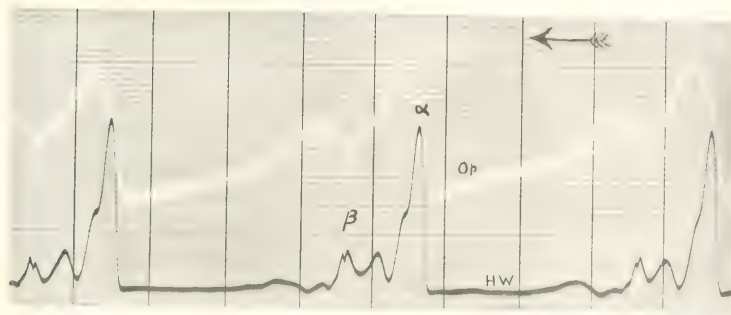


Fig. 8. Synchronised optical (Op) and hot wire (HW) plethograms from a normal subject, showing bifurcated α deflection. Record read from right to left.

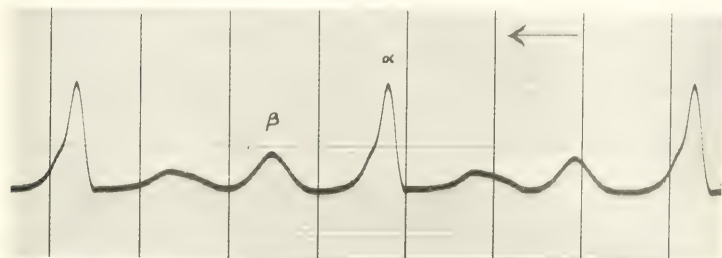


Fig. 9. Radial plethogram from normal subject, showing rounded instead of α deflection. Record read from right to left.

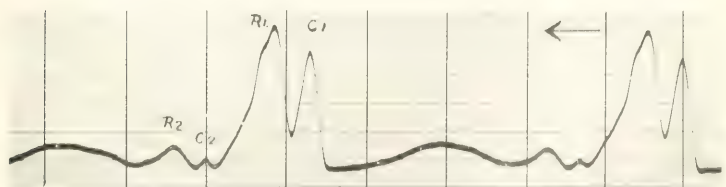


Fig. 11. Carotid and radial plethograms recorded on the same film of the radial anastomosis (From same subject as Fig. 10). C = carotid primary, C = carotid secondary deflection, R = radial primary, R = radial secondary deflection. Record read from right to left.

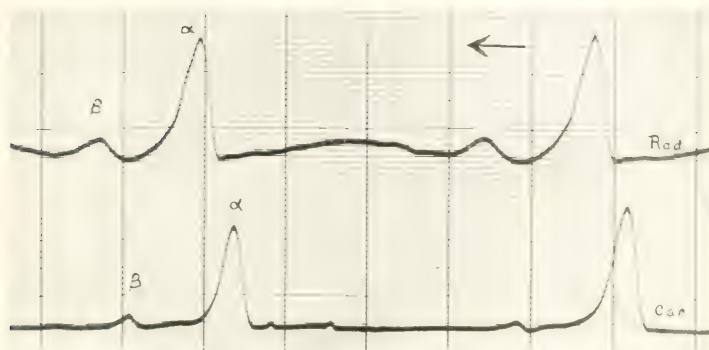


Fig. 10. Strahlgren's parallel (Par.) and radial (Rad.) sphygmograms recorded by acoustic stethescope. α = systolic pressure; β = diastolic pressure. Record begins from right to left.



Fig. 12. Enlargement ($\times 6$) of hot-wire sphygmogram. The point of intersection of the cross lines above letter C is taken for purposes of measurement as the commencement of the carotid upstroke. The two time lines are separated by an interval of 0.2 of a second. Record reads from left to right.

MOVEMENT OF THE HEART'S AXIS WITH RESPIRATION.

By THOMAS LEWIS.*

(*Cardiac Department, University College Hospital Medical School.*)

A FEW years ago, Einthoven, Fahr and Waart² described a method of calculating the electrical axis of the heart by means of electrocardiograms taken from the usual limb leads.

The electrical axis, as ascertained by them, corresponds to that line, in the plane of the leads, along which the greatest potential difference manifests itself. This line of greatest potential difference varies its position during different phases of the cardiac cycle, and may be calculated by the formulæ of these workers for any phase. It should be understood that the electrical axis does not correspond to the heart's anatomical axis, and is at the best but an indifferent guide to it; but it has been thought that the electrical axis may be used to determine *rotation* of the heart's anatomical axis, in that electrical and anatomical axis might be expected to bear a relatively constant inclination to each other. According to this view, if the anatomical axis rotates through a certain number of degrees as a result of mechanical displacement of the heart, the electrical axis for any particular phase of the heart's cycle should show a simultaneous and equal rotation. Such is the conclusion drawn on theoretical grounds in the article discussed.

A recent opportunity has occurred, which seems to make it possible to put this conclusion to the test.

S. T. C., a pensioner of 39 years, was discharged from the army in August, 1918. Having served for two years in the army he was incapacitated by a wound in the chest, on the 14th December, 1917. The bullet entered the chest at the left shoulder and remained deeply buried. He developed a left-sided hæmothorax, which was aspirated, and from which he recovered. An X-ray examination showed the bullet to be lodged in the heart, and his discharge from the army followed because he complained of shortness of

* Observations undertaken on behalf of the Medical Research Council.

breath, exhaustion, and some slight precordial distress on effort, dating from the time of his injury.

Examined on October the 23rd, 1919, he was found to be a spare though well built man. The heart's maximal impulse lay in the 5th rib interspace, well internal to the nipple line. The area of cardiac dulness was not increased. The heart sounds were natural, with the exception of an inconspicuous systolic murmur audible over the maximal impulse in the erect posture. The man presented no signs of heart failure, but by test exercises his breath was proved to be shorter than normal. The pulse, while the man stood at rest, showed an increase of rate (*viz.*, 100 to 120 per minute), and it increased further and readily upon effort.

The physical examination and review of his symptoms lent no support to the view that the presence of the bullet was responsible for his symptoms. No fault could be detected in the heart or circulation, other than those faults which are commonly manifested by patients who suffer from the symptoms summed up in the expressions "irritable heart of soldiers" or "effort syndrome." Repeated screenings of the chest demonstrated the following abnormalities. The movement of the left dome of the diaphragm, though considerable, was limited in its outermost part; it appeared to be a little adherent to the lateral wall of the chest, so that in descending it tended to become concave. Presumably the adherency was the sequel of the old hemothorax on this side. The left side of the chest, however, was equally translucent with the right.

Viewed antero-posteriorly, a complete rifle bullet could readily be seen, lying vertically with its point uppermost; it lay in the silhouette of the heart, about $3\frac{1}{2}$ cms. to the right of the left margin of the ventricle and somewhat nearer the apex than the base of the ventricle. Viewed from the side, the bullet again presented itself in the heart's silhouette; it lay almost vertically, its point inclining a little towards the sternum, and somewhat nearer to the ventral than to the dorsal border of the heart. Its position relative to the chambers was judged from the antero-posterior, lateral and oblique positions; the bullet was thought to lie most probably embedded in the ventricular septum.

Viewed antero-posteriorly, the bullet showed an excursion of about 1 cm. towards the heart's apex during systole; at the same time its axis rotated in an anticlockwise fashion (the chief movement being at its base). Viewed in the lateral position the movements of the bullet with systole were slight.

Viewed both antero-posteriorly and laterally, the bullet was seen to rise approximately 2-3 cms., as the diaphragm moved from a position of deep inspiration to that of deep expiration. In the antero-posterior view its axis was seen to rotate with respiration, the movement being clockwise during inspiration and anticlockwise during expiration.

Rotation of the anatomical axis during respiration. Many attempts were made in October, 1919, to obtain an accurate measurement of the bullet's change of direction with respiration, in the hope of comparing these with the movement of the electrical axis, but these attempts were not completely successful. These earlier observations, nevertheless, have their value.

The patient came again under observation in February, 1923, and the attempts were successfully repeated. Meanwhile the patient had improved in health, being more robust and the heart rate normal. Examined under the X-ray (screening and skiagrams), the bullet was seen to occupy precisely the same position as before, and its movements with the heart beat and respiration were unaltered. Corresponding skiagrams taken during the first period are scarcely to be distinguished from those taken during the second period of observation. The bullet had evidently become permanently and rigidly fixed in the muscular wall of the ventricle.

Three methods of measuring the inclination of the bullet were used. (a) Screening the patient in the antero-posterior plane, the bullet being clearly visible and sharply defined. The preceding observations of the bullet's position and movements is equally applicable to these later observations. As previously stated, the base of the bullet moved during systole about 1 cm., or thereabout, towards the heart's apex, the point of the bullet remaining almost stationary or inclining a little towards the middle line. The movement was rather like that of a pendulum, being executed rapidly: the bullet hung for an appreciable time in the extreme position, corresponding to systole and diastole. The diastolic position appeared to be held the longer. By placing a flat ruler on the screen, its edge could be brought parallel to that of the missile in the diastolic position, and this procedure could be adopted in full inspiration and full expiration, and the inclinations ruled on the screen. So far as the diastole of the heart was concerned, this method was probably accurate within a few degrees. So far as systole was concerned it was found to be more precarious. (b) Instantaneous plates were repeatedly taken while the breath was held in the inspiratory and expiratory positions, the electrical contact being timed by the rhythm of the pulse. Although several helpful pictures were obtained, the method proved too uncertain. It was not possible subsequently to ascertain with certitude at what particular phase of systole and diastole the exposure had happened. (c) The most satisfactory method used was that of exposures of from 4 to 6 seconds, the tube lying 1 metre behind the patient's heart. In many of the plates so obtained, while the chest was fixed in either full inspiration or full expiration, the systolic and diastolic positions of the bullet were sufficiently clearly defined on the plate to allow its axes to be found with an error of not more than one or two degrees. A number of plates taken in this fashion have been compared and are in substantial agreement. The patient was an unusually intelligent man, and was at pains to maintain his posture and uniformly to repeat the inspiratory and expiratory movements.

Movement of the anatomical and electrical axis in the erect posture compared.

Anatomical axis. The patient stood in the erect posture, his sternum resting against the screen.

Method (a). Placing a ruler on the screen the inclination of the bullet in diastole was marked in the full inspiratory and expiratory positions of the chest. These two ruled lines met at an angle of 7.5° .

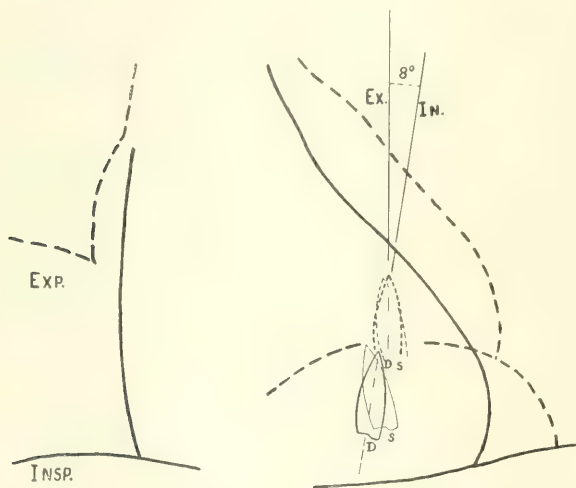


Fig. 1. Outlines of the heart and bullet (half natural size) in full inspiration and full expiration, traced from two X-ray plates taken from the patient in the erect posture. The X-ray tube was at 1 metre distance from the screen.

The unbroken outline represents inspiration and the broken outline expiration. The systolic (S) and diastolic (D) positions of the bullet are shown. The diastolic axis of the bullet moves anticlockwise through 8° in expiration.

Method (c). From two plates, each exposed for 4 seconds in the full inspiratory and expiratory positions, the superimposed tracings of Fig. 1 have been constructed. In this figure the inspiratory contours are represented by unbroken and the expiratory by broken lines. The diastolic position of the bullet (D) is represented by a heavy and the systolic position by a lighter outline. In full inspiration the bullet swung with each systole in an anticlockwise direction through 18° . During expiration it moved up through almost its length, and the swing with the heart beat was about

10°.* In the tracing (Fig. 1), two lines (inspiratory *IN.* and expiratory *EX.*) have been drawn through the axis of the bullet in diastole. They are inclined to each other at 8°. Thus, there is good agreement between the angle of movement in the photographs and the angle measured by ruling on the screen.

Electrical axis. Standard curves were now taken from leads, *I*, *II* and *III*, the patient standing and fixing the chest in full inspiration or

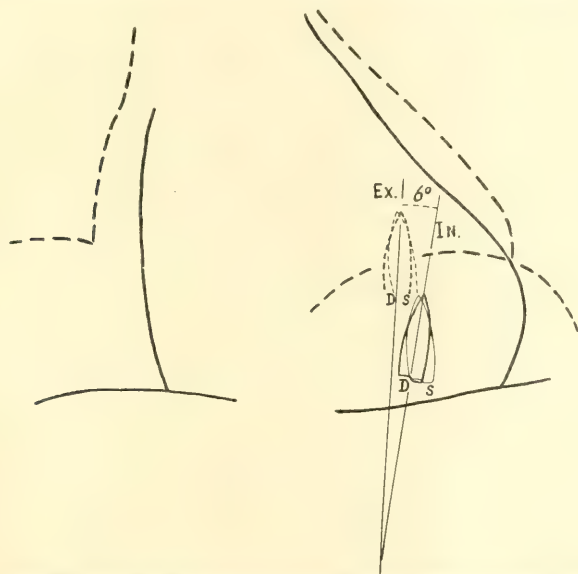


Fig. 2. Outlines of the heart and bullet constructed in the same fashion as Fig. 1. The patient was sitting when the plates were taken. The axis of the bullet moves anticlockwise through 6° in expiration.

expiration. Two complete series of such curves were in substantial agreement and the average values of the summit *R* are given in Table I. The electrical axis of the heart, corresponding to the time at which the summit of *R* was written, is calculated from these data to have been 85°† in inspiration and 76° in expiration. Thus, the electrical axis swung in expiration in an anticlockwise fashion through 9°.

* In some plates it was rather more than 10°.

† The axis passed from above downwards and to the left in the body with an inclination of 85° to the horizontal.

TABLE I.
Height of deflection "R."

	<i>Inspiration</i>	<i>Expiration.</i>
Lead I	4.5	3.5
Lead II	15.5	13.95
Lead III	14.0	10.0
Angle of electrical axis	85	76

Now the summit of *R* in the electrocardiogram comes at the very end of diastole or in the very earliest phase of ventricular systole. It occurs when the ventricles are in a full diastolic position. The respiratory movement of the corresponding electrical axis, therefore, may properly be compared with the respiratory movement of the diastolic anatomical axis. The respiratory movement of the diastolic axis of the bullet* indicates the last. The first is calculated at approximately 9°; the last was ascertained to be approximately 8°.

The two values are remarkably close to each other. The degree of correspondence is more fully appreciated when it is understood that movements of the electrical axis in respiration vary much from subject to subject; the movement varied in the examples given by Einthoven and his collaborators from 4° to 36°.

In so far, therefore, as my observations have been described, they would seem fully to support a contention that a movement of the electrical axis, produced by respiration may be read as meaning a similar movement of the anatomical axis.

Movements of the anatomical and electrical axis in sitting posture compared.

To amplify these observations, a similar series was undertaken with the patient in a slightly different position, namely, while sitting upright in an easy position. This position was chosen after previous experience of the patient's electrocardiograms and their changes with respiration.

Anatomical axis. The movement of the right diaphragmatic dome of this patient was less in the sitting than in the standing posture; on the contrary, the movement of the left diaphragmatic dome was slightly greater. As a consequence, expiration moved the heart more towards the

* The axis of the bullet and a hypothetical anatomical axis of the ventricles will not necessarily correspond; but movement of the one should follow more or less accurately the movement of the other.

middle line in the sitting posture than in the standing. The upward excursion of the bullet in expiration was approximately the same in the two postures of the body; but, whereas in the erect posture the bullet moved a little away from the middle line, in the sitting posture it moved a little towards the middle line. During held inspiration the bullet swung anticlockwise through 13° at the systole; during held expiration it swung in a similar direction through 9° (see Fig. 2).

Lines ruled on the screen along the edge of the bullet at diastole, in full inspiration and full expiration, met at an angle of 8° . The two plates, corresponding to the extreme respiratory positions, showed movement of the diastolic axis of the bullet through 6° (Fig. 2). These two measurements are again in sufficient agreement.

Electrical axis. Two complete series of curves taken from the normal leads while the patient sat in an identical position to that in which the X-ray observations were made (the same stool being used, and a screen being placed against the front of the chest) were in substantial agreement.

TABLE II.
Height of deflection "R."

	<i>Inspiration</i>		<i>Expiration.</i>	
Lead I	2.0		5.0	
Lead II	14.5		11.50	
Lead III	12.5		6.0	
Angle of electrical axis	83°		63	

The values of *R* are given in Table II. The inspiratory angle is calculated at 83° and the expiratory at 63° , representing an anticlockwise movement of 20° in passing from the inspiratory to the expiratory positions; the anatomical axis, as gauged by the axis of the bullet, moved anticlockwise through 6° to 8° . This divergence is beyond the possible limits of error; it was, in fact, quite obvious on simple screening of the patient that the axis of the bullet changed through an angle of far less than 20° , the change was trifling in amount. The electrocardiograms taken in the same posture at a separate sitting gave an anticlockwise movement of 25° (83° to 58°).

To account for this divergence two possibilities suggest themselves. It is possible that the axis of the bullet changed its relation to the anatomical

axis of the heart as a result of change in the shape of the heart during respiration. It appears unlikely that a material change could be produced in this fashion, particularly so since the summit *R* is regarded to result from activity of the lower portions of the septal musculature and the adjoining parts of the ventricles,³ and the bullet lay in this region of the heart. To account for the divergence, therefore, a considerable movement of the bullet relative to the muscle immediately surrounding it must be supposed to have occurred during respiration; such an idea is opposed by the fixity of the bullet; its position had remained unaltered for several years. In a similar case reported by Bond, Phillips and Jevons¹, however, the axis of the bullet moved in a clockwise fashion during expiration, and through such a large angle that it is difficult to understand how the movement could have occurred unless enough leverage were exerted upon the bullet as materially to alter its position relative to the heart wall.

The alternative suggestion is that, in the antero-posterior plane, movements of the electrical axis do not necessarily convey an exact index of movements in the anatomical axis. That a movement of the heart's axis, through a certain angle in the antero-posterior plane, correspondingly influences the direction of the electrical axis by altering the relation of the potentials to the lie of the leads, is a conclusion which we may unhesitatingly accept; but that this is the only fashion in which respiration influences the electrical potentials is improbable. Some small change may result from altered heart rate (the inspiratory rate in this patient was approximately 73 and the expiratory rate 108 per minute); a further and perhaps larger change is certain to result if, during respiration, the heart rotates appreciably around its own axis.*

SUMMARY AND CONCLUSIONS.

1. In a patient in whom a rifle bullet had become fixed in the ventricle, observations have been undertaken upon the movements of this bullet during the heart beat and during respiration.

2. The bullet showed a pendulum-like swing with the heart beat, its base (the lower end) moving conspicuously towards the heart's apex in systole and receding from it in diastole.

3. During expiration the bullet moved almost vertically upwards; at the same time it altered its obliquity to the vertical, the movement being anticlockwise. This change in the bullet's obliquity has been

* Rotation around its axis should have been revealed by the relative positions of the small projection of the bullet at its base (see Fig. 6); unfortunately the shadow of the bullet's base was nearly always in part obscured by the raised dome of the diaphragm in expiration.

measured and the change of angle compared with that occurring in the electrical axis of the heart. The two changes were found to be identical in the erect position of the patient, but showed a conspicuous divergence while the patient sat.

4. It is thought to be improbable that movement of the electrical axis of the electrocardiogram resulting from respiration necessarily gauges accurately the movement of the heart's anatomical axis.

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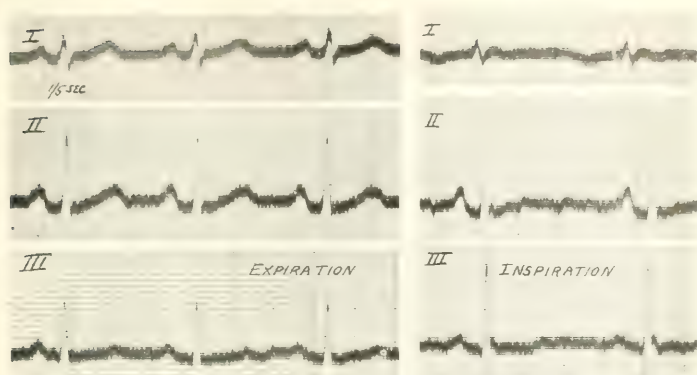
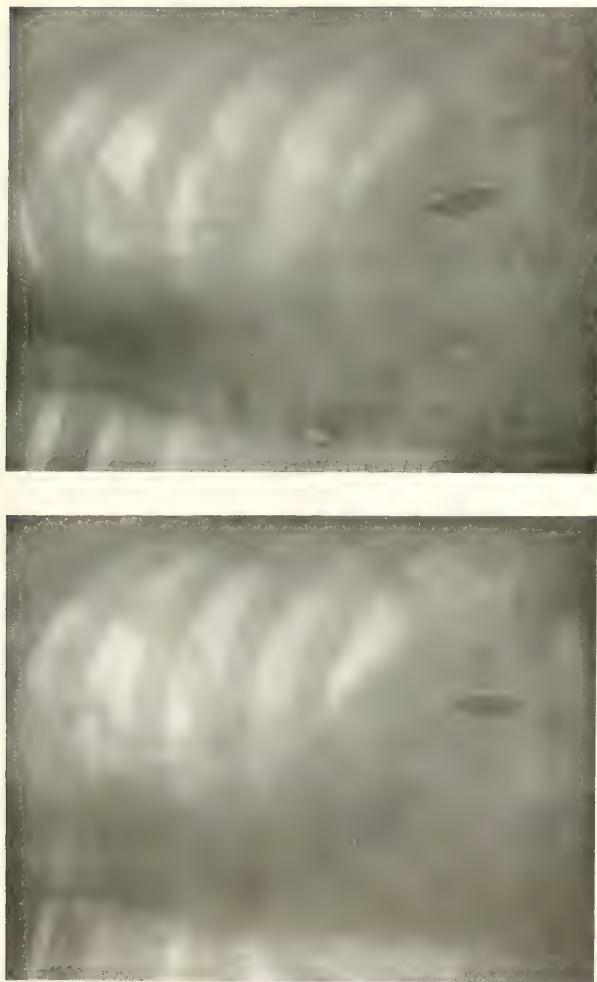


Fig. 3. Electrocardiograms from the three customary leads: the group to the left being taken in full expiration and that to the right in full inspiration; the patient was in the erect posture. Time in fifths of a second. The ordinates are on the scale of 1 cm. = 1 millivolt.



Fig. 4. A skiagraph (half natural size) taken from the patient in the erect posture and during full inspiration. The exposure was 6 seconds; both the systolic (*S*) and diastolic (*D*) positions of the bullet are shown. Used in the construction of Fig. 1.



Figs. 5 and 6 (approx.). For these instantaneous photographs I am indebted to Dr. Robert Knox and to Dr. R. W. A. Schmidt, of King's College Hospital.

The patient was in the erect posture and the photographs were taken while the breath was held in full expiration. The left-hand photograph shows the heart in diastole, and the right-hand photograph shows the heart in systole. Expiration was a little more forcible in the case of the right-hand figure, and this has tended to exaggerate the obliquity of the bullet at the systole.

THE VESSELS CONCERNED IN CLINICAL "CAPILLARY PULSATION."*

By J. J. SUMBAL (of Bratislava).

(From the Cardiac Department, University College Hospital
Medical School.)

THE clinical phenomenon known as "capillary pulsation" was first adequately described by Quincke in the year 1868-70, and was attributed by him to pulsation transmitted from the arterioles into the capillaries. To Quincke's first⁵ and second⁶ account of "capillary pulsation" we owe most of our present knowledge of this phenomenon; he emphasised especially its frequency in aortic disease. Of late years Lombard⁴ and others have shown that certain capillaries of the human skin may be rendered visible under the microscope by adequate illumination, and that the movement of the blood cells in these capillaries can be studied directly. Freeland and Lenhart,² using this method, have watched the blood flow in the small crescent of skin which covers the base of the finger nail and have stated their belief that in cases of aortic regurgitation they have seen the blood flow in the capillaries alter with the beat of the heart. These writers appeared to lack conviction, for, as they explain, owing to rhythmic movement of the whole field of the capillary loops, the events were not easy to follow. The same difficulties are referred to by Jurgensen³, who also believes he has seen a true capillary pulse in a case of aortic disease. These observations have been repeated by Boas¹, who comes to more definite conclusions. He states that at the heart beat the loops of capillaries in the nail bed move forward and that they also move up towards the microscope. Pulsation in the blood column he had not seen, even when the capillaries were submitted to different external pressures.

He considers that previous workers had merely observed movements of the nail bed as a whole or had been confused by these. Boas ascribes "capillary pulsation" to pulsation in the small veins, believing that these pulsate because they anastomose directly with arterioles. He quotes evidence that these anastomoses do exist.

* Observations undertaken on behalf of the Medical Research Council.

Boas's view seems tenable only if it be admitted that the colour of the skin or other structure exhibiting so-called "capillary pulsation" is attributable to the venules rather than to the capillaries; and the last view also Boas appears to accept. Now "capillary pulsation" is a phenomenon which is seen in many parts of the body; thus, it is not only seen in the finger nails and mucous membrane of the lips when these are pressed upon, and in the skin taches obtained by stroking, but it occurs spontaneously in the skin of the forehead and cheeks. There are cases of aortic regurgitation in which the whole face flushes with each heart beat, and so vividly that the flush may be observed at many yards distance. Before accepting the conclusion put forward by Boas it is necessary to acknowledge that all those parts in which the colour waxes and wanes with the heart beat, are coloured by the blood of the venules, rather than by that of the capillaries. This assumption is one with which it is difficult to agree. It is correspondingly difficult to understand, therefore, why pulsatile flow in the capillaries could not be shown without difficulty.

The confusing and general movements of the nail bed seen under the microscope in aortic disease may be largely controlled by lightly embedding the finger in plasticine. Having examined several cases in this way, we came to the conclusion that pulsatile flow in the capillaries may be visible in aortic disease; but it is not seen with sufficient frequency or with sufficient ease to form a convincing and reliable demonstration. A further point arose: the skin overlapping the nail bed is of relatively horny consistence and, as clinical "capillary pulsation" has not been seen to occur in it, it can hardly be stated to occur there, even though it is often witnessed in the flesh under the nail. Consequently, if Boas is right, and the capillaries of this skin do not show pulsation in the blood column, his observation would not disprove clinical "capillary pulsation" to be an event in the capillaries. To prove his case it should be shown that the capillary blood flow is uniform in an area in which the clinical "capillary pulse" is at the moment visible. For this reason the nail was abandoned and the mucous membrane of the lower lip was chosen for further observation.

Method. A block of wood, 2 inches thick and of convenient height and width is fixed vertically and a semicircular gap is cut out of its upper edge to receive the chin of the patient. The gap in the block is heavily lined with plasticine to form a rigid but comfortably moulded bed for the chin. Two upright rods are screwed to the sides of the block, the head coming between them and being securely bound to them with inextensible tapes. The head and jaw are thus securely fixed, while the lip remains free for observation. The microscope is fitted so that its mechanical stage holds a glass slide rigidly, and so that the microscope can be raised or lowered as a whole by means of a fine adjustment. It is placed immediately in front of the holder for the patient's head and lowered until the glass platform comes in contact with the patient's lower lip, on which a little cedar wood oil is placed. The

lip, covered by the glass platform, is thus brought into the field of the microscope: the degree of pressure exerted on the lip is nicely controlled by gradually raising or lowering the whole microscope: such changes in pressure as are introduced throw the capillaries but little out of focus. The field of observation may be changed within sufficient limits by moving the mechanical stage up and down or from side to side. A paper shield guards the lens and glass platform from condensation of water as the patient breathes. The lip is illuminated by a brilliant beam of light thrown from an arc lamp at the side. A plain glass platform, if suitably arranged, serves sufficiently to fix the lip by pressure, and in most instances lateral or forward pulsation of the lip as a whole with the heart beat is avoided: up and down pulsation of the tissues is prevented by the same contact. The avoidance of pulsatile movements of the lips as a whole is imperative, otherwise such pulsation much confuses the interpretation of events seen in the capillaries. When correctly arranged, the capillaries are well seen and remain stationary in the field, and intrinsic movements of them are studied with facility.

Focussing downwards, the capillaries which first come into view are simple loops: they are seen end on or more or less obliquely; some loops are more complex. Under the glass plate, portions of a large number of loops are brought into one focal plane. The lip may be viewed direct at any moment, and thus the observer may be assured while looking through the microscope that clinical capillary pulsation is present in the field observed.

Microscopic appearances of clinical capillary pulsation. The field as a whole, with the lip slightly out of focus, is of a pink colour varying in depth mainly with the degree of pressure exerted. This pink flush also varies in depth with the beat of the heart, the deepest flush appearing a short interval after each carotid pulse. The uniform colour of the lip resolves itself, as focus is changed, into the outlines of capillary loops at varying depths, and attention now fixes itself upon individual loops. The events in these loops vary according to their state of distension, a factor which is chiefly controlled by the degree of outside pressure exerted upon them. If the ends of well distended loops are focussed and these loops are seen on end, these ends have a bulbous appearance. If these irregularly bulbous ends are watched, it is frequent to see in them a perfectly clear rhythmic expansion and contraction with each heart beat. When well distended loops, lying more obliquely in the field, are viewed, rhythmical expansion or contraction of the ends of the loops is usually to be seen clearly, and sometimes it is possible also to define expansile swelling of one or both capillaries forming the limbs of the loop: if seen in one limb only, this is always the afferent vessel: in such instances expansile pulsation in the efferent vessel is more difficult to detect or does not occur. From time to time the dark red bulbous end of a loop appears and disappears in rhythmic fashion, and its appearance and disappearance is not the result of rhythmic change of focus, but is due to filling and emptying. In the more complex loops there may be several

bulbous or angular turning points: in such, the turning points on the afferent side of the loop are often seen to show expansile pulsation, while those on the efferent side may not exhibit it. In less distended loops, presumably those under greater pressure, the passage of blood corpuscles through the capillaries is clearly visible, red and white cells being seen as they flow through. In some capillaries the flow is extremely rapid and is identified mainly by the occasional passage of the more highly refractile white cell; in these pulsatile flow is difficult to recognise. Where the current is less rapid, an acceleration having the rhythm of the heart beat is discerned without difficulty, the rapid flow checks and accelerates regularly. When the flow is slower still, it is not infrequent to see it cease (or even reverse) and proceed rhythmically with the heart beat. These last events are not infrequently seen to occur throughout the whole loop, including afferent and efferent limbs. Attention to the distance separating two capillaries of a loop which lie close together, often shows that these fly a little apart and then fall nearer together again with each heart beat.

According to the lie of the loop and according to its state of distention, one or other of the events described is to be seen in almost every capillary loop in the field, providing that clinical capillary pulsation is visible in the area of mucous membrane under the objective. Acceleration of the blood flow with the heart beat is also seen at times even when capillary pulsation is not visible without magnification.

Pulsations of the kinds described have been clearly seen in the lips of the only 9 cases of aortic regurgitation examined. These cases have been cases of free aortic regurgitation, in the sense that all presented the water-hammer pulse, low diastolic pressures, and high pulse pressures. The events have been witnessed and agreed to by the remaining workers in the laboratory and have been demonstrated to numbers of the hospital students, and to members of the Physiological Society at their meeting on March, 17th, 1923.

SUMMARY.

1. Clinical capillary pulsation of the lip as this is seen in cases of free aortic regurgitation, is found when placed under a 2/3 objective to be a phenomenon of the capillaries themselves. The details of the pulsatile flow in the capillaries are described, as is also the method of examining the lip.

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THE EFFECT OF DRINKING ICED-WATER UPON THE FORM OF THE T DEFLECTION OF THE ELECTROCARDIOGRAM.

By FRANK N. WILSON and RUSSEL FINCH.

(From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor.)

It has been shown repeatedly that local cooling or warming of the surface of the ventricles has a profound effect upon the form of T of the electrocardiogram as well as upon the end-phase of the base-apex electrogram. When the end-phase of the latter is originally negative it becomes positive on warming the apex (Mines²). Warming the apex has a similar effect upon T of the electrocardiogram in axial leads. Cooling the apex, on the other hand, modifies T in the opposite direction (Smith³). The changes in T produced by cooling the base of the right ventricle are the reverse of those produced by cooling the apex of the left ventricle, but are of lesser magnitude. Cooling the surface of the heart greatly delays the recovery from the refractory state of the superficial layers of muscle in the region cooled. The deeper layers of muscle appear not to be affected (Wilson and Herrmann⁴). The changes in T under discussion are not accompanied by changes in the form of the initial deflections (Q , R and S) of the electrocardiogram.

The magnitude of the changes in T , produced in animals by moderate cooling of the apex of the left ventricle, led us to suspect that similar changes might result in man from the drinking of iced-water.

Five experiments were made. The subjects were normal adult men. A control electrocardiogram was made in each instance while the subject was lying on a couch; this posture was adopted because the success of the experiment depends upon the proximity of the fundus of the stomach to the apex of the heart. The subject then drank three glasses (about 600 cc.) of iced-water (temperature about 40°F.) and a second electrocardiogram was made with as little delay as possible. In order to rule out the possible effect of distention of the stomach upon the position of the heart, and hence upon the form of the electrocardiogram, the experiment was subsequently repeated, hot lemonade being substituted for the iced-water. In all experiments the drinking of iced-water produced conspicuous changes

in the form of T in leads *II* and *III*. T of lead *I* was not definitely changed (Fig. 1). T^2 decreased in height and T^3 became inverted or more negative if it was already inverted in the control curve. The effect gradually wore off and disappeared in ten to fifteen minutes. The drinking of a similar quantity of hot lemonade was without effect in all instances. In one instance an ice-pack was applied to the precordium for a half-hour; it had no effect upon the form of the electrocardiogram.

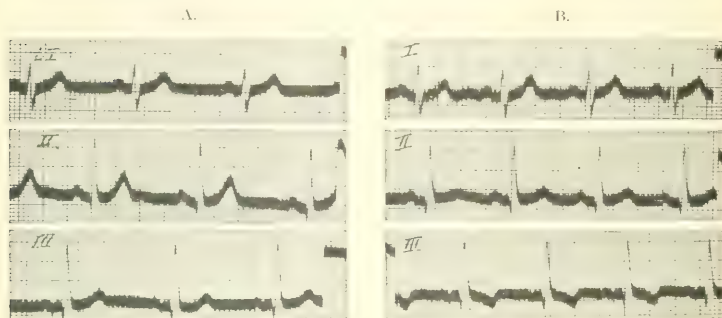


Fig. 1. (—) A. Control electrocardiogram. B. Electrocardiogram after drinking three glasses of iced-water. T^2 is reduced in height and T^3 is inverted; T^1 is not altered.

In order to determine the part of the heart cooled by the iced-water, one of the subjects drank three glasses of a barium mixture and was examined with the fluoroscope while in the same posture used in the experiments. An X-ray photograph was also made, and an outline drawing of the plate is shown in Fig. 2. The blackened area indicates the portion of the heart's posterior surface which came into close contact with the distended fundus of the stomach. Our experiments evidently involved the cooling of the postero-inferior aspect of the apex of the left ventricle. It is clear, therefore, that cooling the apex of the left ventricle produces in axial leads approximately the same effect in man that it produces in the dog.

The most generally accepted explanation of the effects of cooling or warming the apex of the heart upon the form of T is substantially that given by Mines². According to this conception, T is produced by unbalanced electrical forces incident to the decline of the excitation process. All of the ventricular muscle passes into the excited state during the $Q-R-S$ interval, and at the end of this period all of the ventricular muscle is equally active and of the same electrical potential. The return to the resting electrical state does not take place uniformly and simultaneously at all points, so that differences in potential arise, the still-active muscle being relatively negative

with reference to that which has already completed its electric response. The form of T depends upon the order in which various regions of the ventricular muscle complete their electric activity: if the apex of the left ventricle returns to the resting state in advance of the base of the right ventricle T is positive in axial leads: if the base of the right ventricle completes its electrical response in advance of the apex of the left, T is negative in axial leads. Local modifications of the temperature of the ventricular surface alter T through their effect upon the electric response of the muscle affected: cooling prolongs the electric response, warming shortens it.

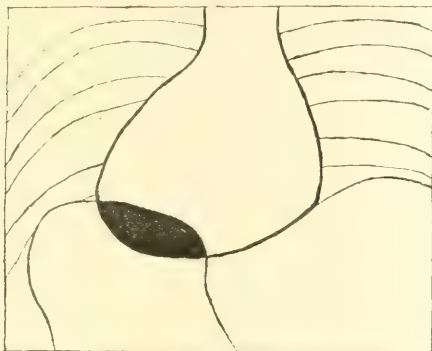


Fig. 2. Outline drawing of Röntgenogram showing the part of the posterior surface of the heart which came into close contact with the distended fundus of the stomach.

It should be noted here that the effect of variations in the temperature of heart muscle upon the form of the electric response has not been worked out in detail. It is possibly similar, however, to the effect of temperature changes upon the (monophasic) electric response of other tissues. Adrian's¹ figures show that cooling greatly prolongs the duration of the electric response of nerve and of skeletal muscle: the rise and the decline of the electric response are both slowed, but the latter is affected much more than the former. The magnitude of the electric response appears not to be greatly modified by changes in temperature.

This explanation of the origin of T and of the effect of local changes in the temperature of the ventricular surface upon it is strongly supported by the work of Wilson and Herrmann.⁴ It must be admitted, however, that many details must be worked out before we shall have an adequate idea of the manner in which this deflection is built up and of the causes of its many variations in form. The effect of drinking iced-water upon the form of the

electrocardiogram is important, so it seems to us, in that it enables us to correlate a definite type of change in T of the human electrocardiogram with a prolongation of the electric response of a known region of ventricular muscle. It may eventually serve as a key to the localisation of the muscle disturbances which so frequently give rise to changes in the form of T in human heart disease. It must be insisted that the changes in T under discussion shall not be confused with those changes in T that accompany changes in the form of $Q R S$. The former may be termed *primary changes in T* ; they are almost certainly due to disturbances in the function of fairly large regions of ventricular muscle. The latter may by contrast be termed *secondary changes in T* : they are secondary to changes in the form of $Q R S$ and have the same significance.

Conclusions.

The drinking of iced-water produces conspicuous changes in the form of T of the electrocardiogram in man. These changes consist in a decrease in the height of T in lead II and inversion of T in lead III , the form of T in lead I is not altered.

These effects are the result of cooling the postero-inferior surface of the apex of the left ventricle, which comes into close contact with the distended fundus of the stomach.

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AN UNUSUAL EXAMPLE OF PAROXYSMAL TACHYCARDIA WITH GRADUAL SLOWING OF RATE.

By H. M. MARVIN.

(From the Department of Internal Medicine, Yale University School of
Medicine, New Haven, Conn.)

PAROXYSMAL tachycardia is a disorder which previous experience has shown to exhibit certain distinctive characters. Of these characters, perhaps the most striking are abruptness of onset and offset and constancy of rate during the paroxysm. The following case is reported chiefly because it illustrates an abnormality which is apparently very uncommon, perhaps unique: the rate of the heart during the paroxysm showed a steady decline over a period of five days, without appreciable change in the underlying mechanism. There are several other points of interest in connection with the case, to which attention will be directed.

History. M. K., a married Russian Jew, of 52, a roofer by occupation, entered the New Haven Dispensary on November the 11th, 1921, complaining of weakness, cough, and shortness of breath. He said that on the previous evening, at five minutes after ten o'clock, his heart had suddenly given a big "thump" against his chest, and then commenced to beat very rapidly. He became greatly alarmed, felt weak, and fainted about five minutes after the onset. He was placed in bed, and soon recovered consciousness, but was unable to sleep all night because of the violent and rapid beating of the heart and a sense of oppression beneath the upper sternum. Shortness of breath became noticeable several hours after the onset. At the time of admission to the dispensary his weakness was less conspicuous, but the palpitation and dyspnoea were slightly greater.

Past history. The patient did not recall any acute illnesses. For the past three or four years he had suffered from a chronic cough, with slight expectoration. This cough was much worse during the winter. He had also been troubled for two years with severe pain in the calves of his legs after walking a short distance.

Examination at that time showed moderate dyspnoea and orthopnoea. There was cyanosis of the lips, but none of the nail-beds of the fingers. The cervical veins were pulsating rapidly, even with the patient sitting upright. There was no abnormal distention of the veins over the anterior thoracic wall or in the upper arms. The thorax showed a definite increase in the antero-posterior diameter; it was hyperresonant throughout; slight prolongation of the expiratory murmur and fine crackling râles were heard at both lung bases posteriorly. The impulse of the heart could be seen and felt diffusely over a fairly large area in the fourth and fifth left interspaces: the point of maximal intensity could not be determined. The left border of percussion dulness was 16 cm. from midsternum in the fifth left space. The sounds were rapid and regular, diminished in intensity and almost tic-tac in quality. The rate was counted at 174 per minute by several different observers. No murmurs or thrills were distinguished. There was moderate sclerosis of the radial and brachial arteries. No pulsation could be detected in the dorsalis pedis arteries. The brachial blood pressure was 90 systolic and 70 diastolic. The liver edge and spleen were not felt. There was no subcutaneous cedema of the extremities or lower back. The temperature was 97.6°, and the respirations were 44 per minute.

The tentative diagnosis was generalised arteriosclerosis, with intermittent claudication from involvement of the leg arteries; arteriosclerotic heart disease; paroxysmal tachycardia; chronic bronchitis and emphysema.

Admission to the hospital was immediate, and the electrocardiogram shown in Fig. 2 was obtained. The rate in that record was 172.7 per minute. A roentgenogram taken with the tube two metres from the patient showed considerable enlargement of the heart in all diameters, most markedly of the left ventricle. The total transverse diameter was 19 cm.; the internal diameter of the thorax was 29 cm..

During the paroxysm the red blood cells numbered 4,640,000, the white cells 13,700 per cubic millimetre on admission, with 69 per cent. polymorphonuclears; the hæmoglobin was 80 per cent. White cells numbered only 10,700 on the second day. The urine was of clear amber colour, acid; its specific gravity was 1.023 to 1.028; it contained a slight trace of albumin at one examination. The sediment showed many urate crystals and on one examination a few white blood cells. The excretion of phenolsulphonethalein in two hours and ten minutes after the intramuscular injection of 1 cc. of the dye was 45 per cent. (normal 60-65). Blood urea nitrogen was 28 mgm. (normal 10-18) and the non-protein nitrogen 53 mgm. per 100 cc. of blood (normal 20-40).

The vital capacity, recorded with a Sanborn spirometer, was 1,400 cc., 32 per cent. of normal.

Clinical course. During the first day of the paroxysm the patient was afebrile, but on the afternoon of the first day the temperature rose to 100.8° (mouth). For the following six days the temperature was slightly,

but constantly, elevated. The range was from 99.4° to 102° , and its tendency steadily downward: it reached normal on the seventh day and remained so until discharge. The heart rate remained constant within two beats per minute, as judged by counts with a stethoscope and frequent electrocardiograms, for three days. During this time repeated efforts were made to stop the tachycardia by means of vagal stimulation: pressure on the vagi in the carotid sheath, pressure on the eyes, repeated rapid swallowing, various

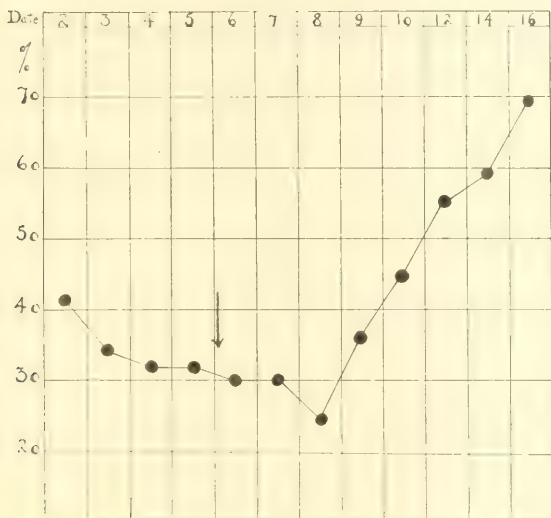


Fig. 1.

Chart showing daily variations in vital capacity. Arrow indicates point at which paroxysm ended.

types of forced respiration, and induced vomiting were all ineffective. On the fourth day the heart rate had dropped to less than 160. An electrocardiogram (Fig. 3) showed a rate of 155.2 per minute. On the following day, the fifth of his stay in hospital, the heart rate was counted at 144, and an electrocardiogram showed a rate of 147. On the sixth day the clinical count was 132 and an electrocardiogram (Fig. 4) showed a rate of 135. On the seventh day the clinical count was 124, but no graphic record was secured. On the morning of the eighth day the rate was found to be 70, and

the electrocardiogram revealed a return to normal mechanism (Fig. 5). The clinical rates as here recorded are those of the writer, confirmed in all instances by other observers.

The patient was discharged on November the 26th, fifteen days after entrance, entirely comfortable except for the cough which had been present for some months. He was observed at frequent intervals in the dispensary until the time of his next entry, his complaints being cough and pain in the legs on walking (he suffered from classical intermittent claudication). At no time did his heart rate exceed 80, and it was always regular except on one occasion when he showed junctional premature beats.

On July the 16th, 1922, eight months after the original paroxysm, the patient reported at the dispensary in very much the same condition as when first seen. His heart rate was 170 and regular; he showed signs of moderate heart failure, with dyspnoea, orthopnoea, moderate cyanosis, râles at both lung bases and slight pretibial oedema. The paroxysm of tachycardia stopped abruptly in the presence of the writer while electrodes were being attached for an electrocardiogram. The patient stated that the attack had started suddenly three days previously at about 9.30 p.m. after the same fashion as the first, and the symptoms during the maintenance of the rapid rate had been identical with those noted during the previous paroxysm: palpitation, substernal oppression, dizziness, slight pain over the liver, dyspnoea and orthopnoea, and increase in the severity of his chronic cough.

Seventeen days later, on August the 2nd, the patient again presented himself with the same signs. He said that a third attack, similar in its onset and symptomatology, had begun in the late afternoon of July the 31st. He had been even more distressed than on the two previous occasions, but was reluctant to enter the hospital, and waited hopefully for a spontaneous cessation. His condition had rapidly become worse, and a physician had persuaded him to seek hospital care.

At the time of this, his second entry, the signs and symptoms were almost exactly as recorded for the first admission. The heart rate was counted at 170; electrocardiogram showed it to be 168 (Fig. 6). With the consent of the patient, he was left without treatment for two days to see if the rate would again fall gradually. At the end of the second day the symptoms and signs of heart failure were increasing so rapidly that repeated attempts were made to end the attack by vagal stimulation. All efforts failed. On the following day, quinidine sulphate was given in doses of 0.4 gm. at 2.30, 4.30, 7.15 and 9.15 p.m. Before the administration of the first dose the heart rate was 166. At 4.30 the rate was 150, at 6.30 it was 144, and at 10.0 p.m. it was still 144. At 1.30 a.m. it had dropped to 70. All of these counts were made at the apex of the heart by the physician in charge of the ward.

A roentgen-ray plate of the heart taken during this paroxysm, at a time when there were conspicuous signs of heart failure, showed the heart shadow to be of the same size and shape as that taken eight months previously

in a similar manner. Another similar plate was taken some days after the return to normal mechanism, when the signs of failure had largely disappeared, and there was no change in the outline or measurements. The absence of enlargement is in keeping with the findings in Levine and Golden's cases².

Observations on the vital capacity were made daily at the same hour by the same observer, and the results are shown in the accompanying chart. The figures represent the percentage which the observed vital capacity bears to the calculated normal, calculated on the basis of surface area of the body⁵. A Sanborn spirometer was used. It will be noted that the vital capacity steadily decreased as the tachycardia continued, although considerably depressed at the time of entrance. This fall in vital capacity continued for three days after the end of the paroxysm, but its rise was coincident with the first clear signs of clinical improvement.

The blood pressure during the paroxysm varied slightly, but averaged about 96 systolic and 68 diastolic. There was but a moderate rise in the systolic pressure after the termination of the tachycardia, the average reading being 108 systolic, 68 diastolic.

The phthalein output during the paroxysm was 76 per cent. in two hours and ten minutes: five days after the end of the tachycardia it had risen to 82 per cent. The urine was constantly negative, as on previous occasions, except for a slight trace of albumin during the stage of congestive failure.

Daily counts of the white blood cells showed a slight but progressive decrease. On the day of admission the total count was 13,500, with 64 per cent. polymorphonuclears. On the four following days the counts were 11,600, 10,500, 10,500, 9,200.

The temperature curve was similar to that obtained during the first visit to the hospital; there was no fever until the late afternoon of the first day in the hospital, when the temperature rose to 100. This was twenty-four hours after the beginning of the paroxysm. For the following eight days it fluctuated between normal and 100.6°, reaching normal on the fifth day after the conclusion of the tachycardia.

There was steady improvement in his clinical condition until his discharge eighteen days after admission. Since that time he has been followed at frequent intervals for almost a year, and there have been no further paroxysms. The heart has remained regular and slow, and the patient's only complaints have been moderate cough and pain in the calves of the legs after walking.

Discussion of electrocardiograms. The electrocardiograms shown in the first three figures were obtained during the original paroxysm.* All of the records which were taken during the first and second paroxysms have obvious similarities in the form of the ventricular complexes, which are

* Owing to lack of definition, these three figures have been redrawn by overlining; the essential details of the original curves have not been modified, however.

highly abnormal. That the ectopic focus in this instance did not lie in the auricle is indicated by the fact that in practically all records auricular waves can be discerned falling with alternate ventricular complexes. They are well shown in leads *II* and *III* of Fig. 3 and in the same leads of Fig. 6. (All records obtained during the second paroxysm showed the characteristics noted in Fig. 6.) The paroxysm is considered to be of ventricular origin, and these inverted auricular waves probably represent retrograde impulses from the ventricle, with delayed conduction through the junctional tissues. Several instances of undoubted paroxysmal ventricular tachycardia with *P* waves following every second ventricular complex have been published, although in most of them the *P* wave was incorporated in, or followed very closely, the end of the ventricular complexes^{1, 3}.

No similar case has come to our attention in a review of the reported cases of paroxysmal ventricular tachycardia, although Wolferth and McMillan⁷ and Strong and Levine⁴ have recently re-emphasised the fact that variation in the rate of the paroxysm may occur. It seems to be particularly apt to occur during the few seconds immediately following the onset of the new mechanism. One case illustrating a "rapid, but not immediate," onset and offset has been published by White⁶, but the increase and decrease in rate in his case covered a period of only one or two seconds.

It is of interest to note the connection of fever with the paroxysms. During both of the reported paroxysms, and also during a third short one which was observed but is not here presented, there was moderate fever which began after the onset of the tachycardia and persisted for several days after its termination. There was no demonstrable evidence at any time of an infection other than the chronic bronchitis which had been present for years, but there was a moderate leucocytosis (13,500) which quickly disappeared. It seems unlikely that the attacks were precipitated by an acute infection, in view of the absence of all symptoms before the onset and of the failure of fever to appear until eighteen hours or more after the paroxysm had begun. Levine and Golden² noted fever and leucocytosis in a number of their cases, and felt that the abnormal findings were to be attributed to the cardiac disturbance rather than to an infection.

SUMMARY.

A case of paroxysmal tachycardia is reported in some detail, with electrocardiograms which are thought to indicate a ventricular origin. The interesting feature of the case is the gradual slowing of the rate from 172 to 124 over a period of five days, without change in the fundamental mechanism as shown by electrocardiograms. A curious febrile reaction was witnessed during the paroxysms. During the paroxysms a progressive decrease in the vital capacity of the lungs was noticed, with subsequent recovery, but the heart did not change in size.

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(All reported cases of paroxysmal ventricular tachycardia have been collected so recently by Wolferth and McMillan (⁷), with complete references, that it has not been thought necessary to repeat the additional references in this connection.)

THE EFFECT OF BLOOD PRESSURE ON THE EXTENSIBILITY OF THE HUMAN ARTERY.

By J. CRIGHTON BRAMWELL,* A. C. DOWNING and
A. V. HILL.

(From the Physiological Laboratory, Manchester.)

THE extensibility of an artery can be measured by the velocity of the pulse wave in it. In a recent paper² Bramwell and A. V. Hill gave an account of an experiment, made by simple mechanical recording, on the velocity of the pulse wave in an isolated human artery at different blood pressures. It was shown, as had been calculated from Roy's observations³, that the velocity was low at low pressures, and increased as the pressure was raised, attaining very considerable velocities at the higher pressures. In a subsequent paper Bramwell, McDowall and McSwiney⁴ showed, on living man, over the range of pressures from zero up to diastolic, that the same type of increase of velocity with pressure occurs.

The apparatus previously employed by Bramwell and Hill, for observations on an isolated artery was comparatively crude, and was not easy to use. Since we wished to take the opportunity, provided by the post-mortem room of the Manchester Royal Infirmary, of making observations on the isolated arteries of a number of human subjects it was desirable to adopt a less difficult and more accurate method. This has been based on the use of two hot-wire sphygmographs, employed with the two strings of an Einthoven galvanometer. The first hot-wire and string mark the arrival of the wave at one end, and the second hot-wire and string its arrival at the other end of the piece of the artery used, the pair of strings recording together on a rapidly moving photographic plate. For purposes of measurement the records were projected, by means of a lantern, on to a large sheet of mm. squared paper and could be read to about the nearest 0.0003 of a sec.

* Working for the Medical Research Council.

Details of apparatus and methods of use. The apparatus is shown in Fig. 1. Two thick brass tubes are clamped horizontally in carriers fixed on a heavy block of wood. Each ends in a detachable "adaptor," which can be screwed tight to the tube by a heavy brass nut, care being taken to eliminate any space where air bubbles might collect and contaminate the results. There are three pairs of adaptors, to fit small, medium and large arteries. The ends of the artery are slipped over the appropriate adaptors and firmly tied with thread. The adaptors are then tightly screwed to the ends of the tubes. The tubes are unclamped and adjusted so that a slight tension is applied to the artery and then clamped firmly again, long flexible rubber pipes being attached to their ends. Mercury is then run backwards and forwards through the whole apparatus, sweeping all air bubbles in front of it, and filling the tubes and the artery. At one end is a vertical glass tube, with a scale on which the pressure in the artery can be read in mm. of Hg.; at the other end is a reservoir, which can be raised and lowered to vary the pressure as desired.

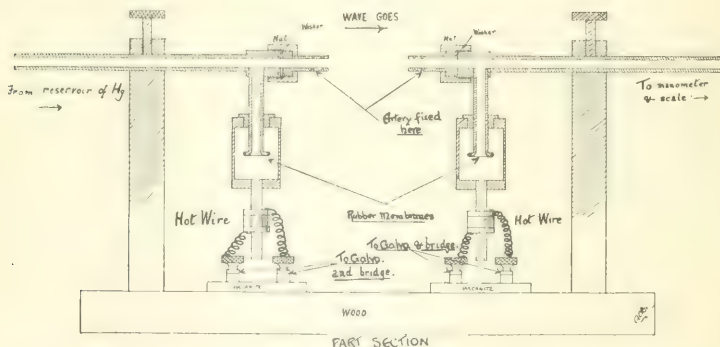


Fig. 1. Instrument employed for measuring time of transmission by means of two hot wires.

Into the brass tubes, close to the adaptors, are screwed and brazed two side pipes. These pipes open out into small brass tambours, over which thin rubber is tightly stretched. The wave to be recorded causes a sudden bulge in the rubber membrane, which blows a sudden puff of air down the tube of a hot-wire sphygmograph, screwed into a brass cover placed over the side tube and tambour. This causes a sudden deflection of the string galvanometer in the manner described elsewhere². The wave coming from left to right causes a deflection in the left-hand sphygmograph almost immediately before it enters the artery; it passes across the artery, and almost immediately after reaching the other end of the artery it causes a deflection in the right-hand sphygmograph. The interval between the two

upstrokes of the record is approximately, therefore, equal to the time taken in traversing the artery. It is only necessary to make a small zero correction, which is determined once for all (for each pair of membranes and adaptors) by connecting them end to end with a piece of rubber tube and determining the interval required by a wave to traverse the now practically rigid pipe. This zero correction was only 0.0025, 0.0022, and 0.0047 sec., for the large, medium and small adaptors respectively, with the particular membranes used in this series of experiments.

The wave employed is obtained by giving the rubber pipe attached to the brass tube a sharp blow with the hand. Various mechanical devices were tried, but this seems to be the best method of setting up the type of wave required. It is necessary to avoid shaking the instrument, otherwise subsidiary vibrations appear on the records. The rubber, therefore, at the point where it is struck, lies upon a very heavy block of lead, supported on a

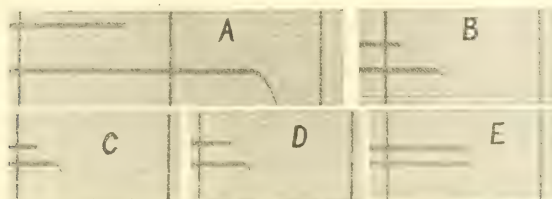


Fig. 2. Typical records obtained from the instrument of Fig. 1, employed with the two copper strings of an Einthoven galvanometer. Magnification about 60. Time marks in 1/10 secs. Read from left to right. The upper line in each record shows the arrival of the wave at the left-hand tambour. A, B, C and D records obtained from a human artery. A, low pressure (15 mm.); D, high pressure (250 mm.); B and C, intermediate pressures. E, a determination of the zero correction, when the adaptors were connected directly end to end.

separate though neighbouring table. The wave having to pass through the rubber tube before entering the brass pipe, the blow should be sharp and delivered at a point not more than 10 or 20 cms. from the brass pipe: otherwise the upstrokes of the records will not be sufficiently sudden and measurement will be less accurate. The photographic records need only be about 2 cms. wide. Merely the commencement of each upstroke is required, and the strings may be brought very close together by adjusting the bridges of the hot-wires. We have usually made four records on each plate. The upstrokes should be in opposite directions, and outwards for safety. A set of typical records is given in Fig. 2.

The actual measurement of the length of an artery provided what might have been a difficult problem. It is not easy to define its unextended

length." The actual distance traversed by the wave can, of course, be measured to the nearest 0.1 mm., but if the artery be stretched this is not the unextended length. Filled as it is with mercury the artery tends to sag, and, although we have usually supported it, it is quite impossible to say when it begins to be stretched lengthways. Fortunately, however, we have found, both in control experiments on rubber pipes and on human arteries, that the actual velocity observed, viz. (distance between ends of adaptors) \div (corrected time interval), is independent of the degree of longitudinal extension, over a much wider range of extensions than would ever occur in an actual experiment. Consequently we have been able merely to stretch the artery to a convenient extent, *i.e.*, until it lay evenly between its ends, and then to measure the actual velocity in it as it lay.

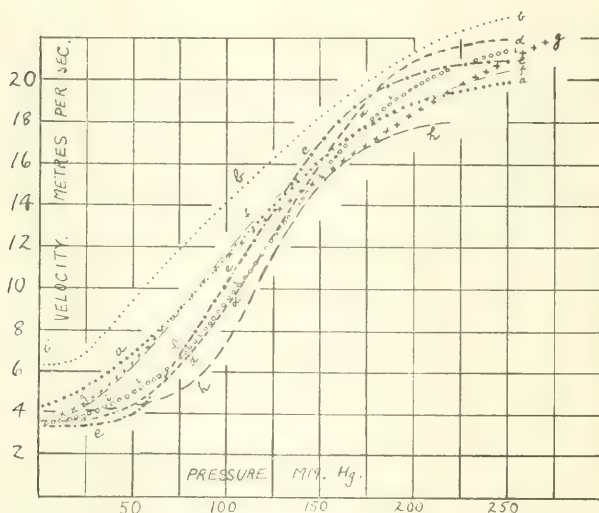


Fig. 3. Relation between pulse wave velocity and pressure in eight "normal" individuals.

As pointed out by Bramwell and Hill², the use of mercury inside the artery instead of blood has the advantage of giving a time interval 3.58 times as long and, therefore, much more accurately measurable. It is, moreover, much cleaner to use than any other fluid, and in the short time occupied by an experiment is not likely to injure the artery. The velocities given below have all been calculated for the case of blood, by multiplying the observed velocities by 3.58. The artery employed was the carotid, and

the records have generally been made on the day of the autopsy. The arteries were suspended in isotonic saline solution till required: no disinfectants or other reagents were employed.

In nearly all cases observations of the velocity were made at twelve different pressures, ranging from 15 to 250 mm. of Hg.. In some cases measurements were made on both carotids of the same individual, and good agreement attained.

Even the sharpest upstroke is to some degree rounded off and a convention is necessary as to the point defined as its commencement. On the magnified image employed in measuring the records a pencil line was drawn as closely as possible down the middle of the upstroke. The point where this line met the continuation of the previous base line was adopted throughout as the commencement.

Results. The results are best shown in diagrammatic form. It is unnecessary to give the actual observations, as the curves drawn through them fit with almost complete accuracy, and there are about twelve observed points on each curve.

Fig. 3 shows the results of observations on what may, for the present purpose, be called "normal" individuals, *i.e.*, individuals in whom there was no gross post-mortem evidence of arterial disease, and who had not suffered from a long and wasting illness. The following are details of the cases:—

<i>a</i>	G. H.	Aged 44	Cerebral hæmorrhage.
<i>b</i>	J. H.	„ 66	Lobar pneumonia.
<i>d</i>	R. W.	„ 14	Acute rheumatic carditis.
<i>e</i>	G. P.	„ 14	Encephalitis lethargica.
<i>f</i>	J. P.	„ 45	Antimony poisoning.
<i>g</i>	T. J.	„ 43	Died after nephrectomy.
<i>h</i>	C. W.	„ 8	Empyema.
<i>i</i>	H. P.	„ 36	Septic meningitis.

These cases may be subdivided into two groups (*i*):—*d, e, h* and *i*, all of which exhibited a highly characteristic form of curve, and (*ii*):—*a, b, f* and *g*, which gave curves intermediate in form between the normal type and the pathological type described below. Of the latter *a* died on the day after admission to hospital, and although his arteries exhibited no gross change, post mortem there was considerable cardiac hypertrophy which was not accounted for by the presence of any valvular lesion or renal disease. This suggested that the high systolic pressure (200 mm.) recorded during life had been present for some time, and was not merely the result of increased intracranial tension; *b* exhibited a moderate degree of atheroma of the

aorta, though this was, perhaps, not in excess of what is frequently met with in hospital patients of this age who die of some disease not directly associated with the cardio-vascular system. In the case of *f*, apart from his age (46), there was no reason to anticipate any divergence from the normal type of curve: *g* was a somewhat emaciated subject who had been suffering from tubercular disease of long standing.

Of these eight curves the highest and straightest, and the one which rises most rapidly from the start, is *b* on the oldest individual; the lowest and the one with the most obvious S-shape is *h*, on the youngest individual. At 70 mm. pressure (taken as corresponding to an average value for the diastolic pressure) the order of increasing velocities with different ages is:—

Order.	<i>h</i>	<i>e</i>	<i>d</i>	<i>i</i>	Equal.			<i>b</i>
					<i>f</i>	<i>a</i>	<i>g</i>	
Age	8	14	14	36	45	44	43	66

The order of ages corresponds to that of velocities. Hence the velocity of the pulse wave (at or near the diastolic pressure) increases, and the extensibility of the artery diminishes with age, as has recently been shown by Bramwell, Hill and McSwiney³ on a number of normal living individuals.

A "mean" normal curve, so far as it is justifiable to talk of a "mean," is given in the full line of Fig. 4. Its form is quite characteristic. At low pressures it runs horizontally as the pressure rises, then begins to turn up at a point rather below the normal diastolic pressure, rises most rapidly in the neighbourhood of the normal diastolic and systolic pressures, and then tends to rise less rapidly as the pressure is further increased. We will discuss the cause and the consequence of this type of curve later: for the moment we will consider merely its occurrence in "normal" arteries. It appears in every one of the eight cases shown in Fig. 3, most characteristically in the child of 8 and in *d*, *e* and *i*, least characteristically in the man of 66 and in *a*, *g* and *f*. In Fig. 4, for comparison with the "mean" normal curve, are given observations on three subjects in whom the arteries might possibly have been expected to be abnormal:—

<i>a</i>	R. H.	Aged 43	Carcinoma of the pylorus. Very emaciated.
<i>β</i>	J. D.	.. 70	Advanced atheromatous changes in the aorta and cerebral vessels.
<i>γ</i>	T. F.	.. 34	Septicæmia and emaciation.

For comparison are included observations on the arteries of:—

8, G. R., which by mistake had been placed in dilute formalin after removal from the body.

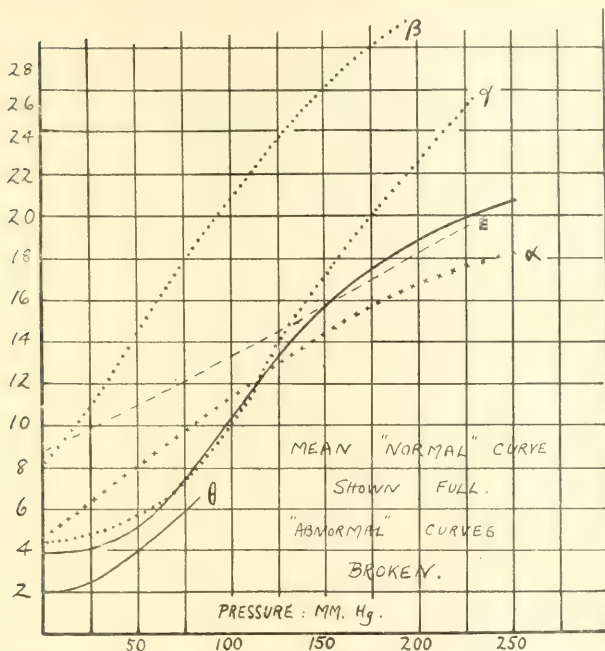


Fig. 4. Relation between pulse wave velocity and pressure. Full line, "mean" normal curve; broken lines, abnormal cases described in text. θ , curve from normal living individuals given by Bramwell, McDowall, and McSwiney.

It is obvious that γ conforms to the usual type of curve, at any rate at low pressures. α and β , however, as also ϵ (which had presumably lost its elasticity to some degree as a result of the formalin) show a complete and important departure from the normal type, a departure suggested by a , b , f and g of Fig. 3. They give no horizontal portion and rise steadily as the pressure is increased. The S-shape of the curve is presumably a characteristic of normal arteries which retain their elasticity; the absence of the S-shape, in the region below the usual diastolic pressure, is associated with changes which have deprived the arteries of their elasticity. The most notable divergence from the normal curve is β where atheromatous change in the artery produced enormously high pulse wave velocities.

It is possible in living man, as shown by Bramwell, McDowall and McSwiney⁴, to construct a curve similar to those given in Figs. 3 and 4,

relating pulse wave velocity to internal pressure. Their results are indeed not of the same accuracy as those obtained on the isolated artery: they involve certain assumptions as to the constancy of the velocity in different arteries, and they cover only the range of pressures from zero to diastolic. The important region, however, in which the characteristic horizontal portion of the curve occurs, lies below the diastolic pressure and so can be covered by their method. Moreover, by placing nearly the whole upper limb in a suitable bag or chamber, where the pressure could be varied at will, the accuracy would be much improved and the assumptions eliminated. It is obvious, therefore, that a method is available by which the elastic

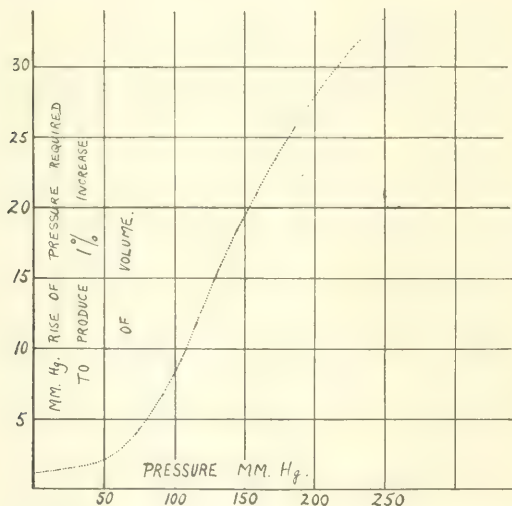


FIG. 5. Mean curve of Fig. 4 recalculated to give the instantaneous relation between the rigidity of an artery and the blood pressure.

condition of the artery of a living man can be investigated, over the range of pressures within which degenerative changes produce their most characteristic effect.

The "typical experiment" of Bramwell, McDowall and McSwiney⁴ on a normal living man is shown as *o* in Fig. 4. It is similar in character to the mean normal curve, but lower and less obviously S-shaped. Whether the difference be due to the fact that they investigated the brachial while we have investigated the carotid artery, or whether it be due to the presence

of living smooth muscle in their case but not in ours, it is impossible at present to say.

Theoretical. We will consider finally the form of the normal curve relating the pulse wave velocity to pressure. It was shown by Bramwell and Hill² that the velocity is related to the elasticity by the formula,

$$V = 3.57 \sqrt{\text{mm. Hg. rise of pressure required to produce 1 per cent. increase in volume.}}$$

In Fig. 5 the mean curve of Fig. 4 has been recalculated to give the relation between y —mm. Hg. rise of pressure per 1 per cent. increase of volume (what we may term the "rigidity" of the artery), and x —pressure in mm. Hg..

At 80 mm. pressure a 5 mm. rise of pressure causes a 1 per cent. increase in the volume of the artery. At 50 mm. pressure only a 2 mm. rise of pressure is necessary, while at 110 mm. pressure over 10 mm. rise, at 150 mm. pressure nearly 20 mm. rise, and at 200 mm. pressure about 28 mm. is required to produce the same expansion. We see the enormous effect exercised by a rise in the diastolic pressure, upon the ease with which the arteries accept the blood ejected by the heart.

It is possible by numerical integration to construct from Fig. 5 a curve relating the total volume of an artery to the pressure inside it. At first sight it might have been supposed that such a curve could better be made directly, as was actually done by Roy⁶. As pointed out, however, by Bramwell and Hill², the "after extension" of living tissues, *i.e.*, the fact that a tissue goes on stretching for some time when subjected to a constant stress, invalidates readings so obtained if they be required to represent the extension resulting from a sharp momentary stress, such as follows the heart beat. The actual curve obtained by integration is shown in Fig. 6. Here, on an arbitrary scale of volumes, the volume of an artery is plotted against the pressure inside it. At zero pressure the artery collapses; this limit is not practically obtainable, hence the curve is not continued below about 10 mm. pressure.

In normal man the ejection phase of ventricular systole lasts for about 0.3 sec., which is more than enough to allow the pulse wave to reach the extreme end of all the arteries. Hence at each beat the blood forced into the aorta by the heart expands the arteries all over the body. If we knew the total volume of the arteries, *i.e.*, of all the vessels into which the pulse wave could be assumed to penetrate, and if the extensibility of all the different arteries were the same* (and could, therefore, be calculated from observation on the mean velocity of the pulse wave) we could calculate the output of the heart from the pulse pressure. We do not wish to suggest that

*The differences in structure between the larger and smaller arteries as well as the experimental observations of Bazett and Dreyer¹ suggest that this is not the case.

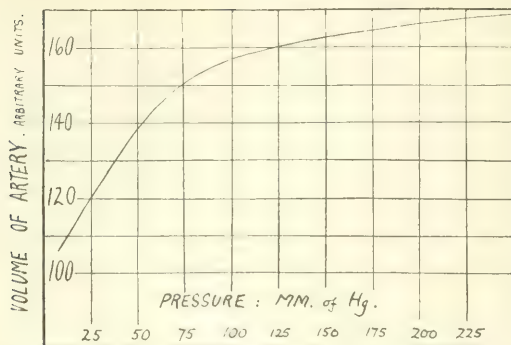


Fig. 6. Relation between volume and pressure in the "mean normal" artery of Figs. 4 and 5, when subjected to a sudden change of pressure.

such a calculation can actually be made quantitatively, because it would involve the further assumption that the amount of blood escaping through the capillaries during the ejection phase of systole is negligible as compared with the total ventricular output, and this is not true. But although the actual values given below are purely hypothetical, they serve to illustrate more clearly a general relationship between cardiac output and pressure which undoubtedly does exist and is of considerable importance. Let us assume that an individual of 70 kilos. weight has, at any moment, 1,500 cc. of blood in his arteries and that Fig. 6 represents the normal volume pressure relation. Then the following table will give the output of the heart per beat for various pulse pressures.

TABLE I.

Output per beat for the "normal individual" of Figs. 4, 5 and 6 for different pulse pressures at different diastolic pressures.

Diastolic pressure, mm.	50	70	75	80	100	125	150	175
Output cc. (pulse pres. 25 mm.)	130	73	64	55	30	24	17	15
" " (" " 50 mm.)	200	110	97	83	55	41	31	28
" " (" " 75 mm.)	230	134	122	105	72	56	45	40
" " (" " 100 mm.)	260	155	139	125	87	70	57	—

We see that at low diastolic pressures a very considerable output is attained for quite a small pulse pressure, while at high diastolic pressures the output remains small even for very high pulse pressures. Clearly it is

impossible for an individual with a high diastolic pressure to attain a considerable output per beat without developing a dangerously high pulse pressure, and throwing an enormous strain on the heart. Conversely it is obvious that an individual with a low diastolic pressure will be able to reach a high output without difficulty. Many observers have found, by other methods, an output of about 100 cc. per beat in normal man. At a diastolic pressure of 70 mm. this is attained in Table I, by a pulse pressure of 44 mm., at a lower diastolic pressure by a considerably smaller one. Hill and Lupton⁵ have recently shown that during running an output of at least 200 cc. per beat can be attained: as the result of exercise, however, the ejection phase becomes a much larger fraction of the whole cycle, and during that phase an appreciable portion of the whole output passes away through the capillaries and so relieves the heart from the high systolic pressure it would otherwise have to meet. The same relative increase in the ejection phase may be of importance in abnormal conditions.

(One fact clearly brought out by Table I is that, quite apart from the danger of damaging the arteries by a high pulse pressure, or the heart by excessive activity, no individual with a high diastolic pressure such as 125 or 150 mm., could possibly take hard exercise for any length of time. He would inevitably suffer from oxygen want. Without some such compensating mechanism as polycythemia an output of 50 cc. per beat could not possibly provide the body, even at a pulse rate of 180, with more than about 1,500 cc. of oxygen per minute, an amount required in a healthy man to walk at the rate of about $4\frac{1}{2}$ miles per hour.

The velocity of the pulse wave in living man has been determined, between points on the right carotid and the right radial arteries, by Bramwell, Hill and McSwiney³ on a number of different individuals of ages varying from 5 to 80, and a mean curve given. It is obvious from Figs. 3 and 4 that the diastolic pressure is a very important factor in determining the velocity of the pulse wave, but if we read off from the curves of Fig. 3 ("normal individuals") the values of the pulse wave velocity at 70 mm. pressure, these should not be far different from those existing in similar normal individuals during life. The results are as follows:—In the fourth line are values (called "velocity from curve") read off for the corresponding age on the curve given by Bramwell, Hill and McSwiney.

Individual	<i>h</i>	<i>d</i>	<i>e</i>	<i>i</i>	<i>g</i>	<i>a</i>	<i>f</i>	<i>b</i>
Age in years	8	14	14	36	43	44	45	66
Velocity metres per sec.	4.9	5.8	5.7	6.2	8.5	8.4	8.2	11.4
Velocity from curve	5.3	5.7	5.7	7.0	7.3	7.4	7.4	8.1

The agreement is good: apart from the last entry there is no consistent difference between the value measured on the isolated carotid artery, at a

pressure of 70 mm., and that obtained between carotid and radial on a living man of the same age. Neglecting *b*, the average difference is only 0.7 m.p.s., which is not greater than the average variation between normal individuals of the same age.

In our discussion we have neglected throughout any possible influence, during life, of the smooth musculature of the arterial wall. In some of the smaller arteries, where the amount of such muscular tissue is considerable, appreciable changes in extensibility may possibly result from alterations in its activity. Clearly the matter requires fuller investigation in the live animal: here we have discussed the fundamental mechanical properties of such an artery as the carotid, which is endowed with relatively little muscle.

SUMMARY.

A method of measuring the pulse wave velocity in a few cm. of isolated artery, at any desired pressure, is described. The results obtained on the carotid arteries of twelve human subjects are given. The normal relation between extensibility and pressure is described, and examples of the effects of degenerative changes are given.

The relation between the pulse pressure, the output per beat, and the diastolic pressure is discussed, and it is shown that a considerable output is impossible at a high diastolic pressure.

We have to thank Prof. J. Shaw Dunn for the facilities which he has afforded us for obtaining the material on which these observations were made.

The expenses of this research have been borne in part by a grant (to A. V. H.) from the Government Grants Committee of the Royal Society.

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OBSERVATIONS RELATING TO ARTERIO-VENOUS ANEURISM.

PART I.—CIRCULATORY MANIFESTATIONS IN CLINICAL CASES WITH PARTICULAR REFERENCE TO THE ARTERIAL PHENOMENA OF AORTIC REGURGITATION.*

By T. LEWIS and A. N. DRURY.

(*From the Cardiac Department, University College Hospital Medical School.*)

IN the present article we record a number of observations upon cases of arterio-venous aneurism, resulting from wounds received during the recent war. Our object in investigating these cases has not been solely to extend the knowledge of the circulatory changes occurring in conditions of arterio-venous anastomosis; chosen cases seemed to us to offer a fruitful field in which to investigate certain arterial phenomena which are generally recognised to occur in defective closure of the aortic valves.

If blood leaks from the arterial system through channels other than the natural pores provided by the capillaries, and leaks out in sufficient quantity and at a sufficient rate, such leakage will change the arterial pressures. So far as many physical signs are concerned it seems to be a matter of indifference whether the leak occurs back into the ventricle, into the pulmonary artery through a patent ductus arteriosus, or into a vein through a direct anastomosis. The leak produces certain changes in the arterial pressures which are common to all these pathological conditions. That the arterial changes should be identical *in all respects* in these three separate conditions, however, is scarcely to be expected; for the leakage in aortic regurgitation is confined to diastole, while in arterio-venous anastomosis and patent ductus arteriosus it occurs throughout the whole cardiac cycle. A leakage into a large vein or into the pulmonary artery may also produce different effects from

* Observations undertaken on behalf of the Medical Research Council.

those of reflux into the ventricle, by altering the pressures in these vessels rather than in the left ventricle. Despite these differences, there will remain on the arterial side certain common manifestations of leakage and the phenomena accompanying such leakage in one condition may illuminate similar phenomena occurring in another.

Methods.

All observations recorded in this paper have been taken from patients after a sufficient period of rest and, unless stated to the contrary, with the patient supine.

To obtain records of the pulse's form we have used Wigger's apparatus, the essential portion of which consists of a very sensitive Frank's optical capsule. Measurements of these curves have been made with a Lucas comparator.

Arterial blood pressure readings have been taken by means of a Riva-Rocci sphygmomanometer, palpation of the distal artery being used in the case of systolic popliteal pressure, and auscultation and palpation in the case of pressures in the brachial artery.*

Venous blood pressures have been obtained by means of Hooker's apparatus⁹, which reads in centimetres of water the pressure needed to collapse superficial veins. Such readings have been supplemented in several cases by direct manometric readings, using Moritz and Tabora's method¹⁴. All the readings have been taken with the patients stripped, the precise level of the vein below the patient's sternum being noted in each instance.

To obtain an accurate measure of the size of the heart we have used Levy-Dorn's Orthodiagraph (Groedel's modification). The measurements taken have been the distances of the right and left margins from the middle line, and the longitudinal diameter from the junction of the right auricle and superior cava to the apex of the heart. All these measurements were taken in the anteroposterior position with the patient sitting erect and holding the breath in slight inspiration.

For sound records we have used the string galvanometer in combination with a sensitive microphone and transformer.

The method used for additional observations will be described in the appropriate places.

In the following pages we report our observations upon two cases fully, and direct attention especially to *Case 1*. Observations upon several other cases are more briefly recorded; they were less extensive but form confirmatory evidence in certain particulars.

* Diastolic pressure has been taken to be the point at which the sounds diminish in intensity.

CASE I.

A. V. E., a clerk of 34 years, first came under observation on February the 1st, 1923.

He joined the army in June, 1915, a perfectly fit man of 26 years: he stood his training well and served in France from January, 1916, to August, 1917, when he was wounded in the right thigh by a rifle bullet. He was in hospital for six months and was discharged from the army in March, 1918. He complained of a swelling in the right thigh and heaviness of this leg, which ached a lot after he had walked slowly for half-an-hour. He had noticed palpitation on mounting stairs or after walking some distance. Occasionally, towards the end of the day, giddiness was noticed, and he was bothered by noises in his ears which he attributed to his leg. There had been no past illnesses.

February the 1st, 1923. Physical signs. The patient, a man of 5 feet 5½ inches in height, weighed 112 lbs. Over Scarpa's triangle a very distinct fullness and vigorous pulsation existed. A small round scar was seen at the inner and lower part of the triangle and a larger second scar on the outer side of the thigh on the same level; these marked the track of the bullet. The pulsation was expansile and extensive, almost filling the triangle and extending above Poupart's ligament. A cylindrical swelling was felt throughout the triangle and extended a couple of inches into the abdomen above the ligament. An intense and continuous thrill, easily felt through his clothing, was perceptible from this point in the abdomen to within a hand's breadth of the knee. The maximal area of thrill was in the lower half of the triangle, and it was evident that a communication existed between the superficial artery and vein. The pulsation of the right common femoral artery was much more vigorous than that of the left. The pulses in the two dorsalis pedis and posterior tibial arteries were distinct. The pulsation in the arteries of the right foot disappeared on obliterating the right common femoral artery.

The chest was a narrow one. The outer limit of the cardiac impulse lay 5 cm. beyond the nipple line in the 5th and 6th spaces and the corresponding ribs moved forward a little in systole. The left limit of cardiac dullness agreed with the position of the impulse; the right border lay 2 to 3 cm. to the right of the mid-line. The electrocardiogram was of normal form in all leads. The pulses were conspicuously water-hammer in quality and the carotids throbbing; capillary pulsation was intense; the pistol-shot sound was audible in the brachial and femoral arteries and the pulse in the palms of the hands.

The heart sounds were natural, with the exception of a short systolic murmur at the mitral area and at the pulmonary cartilage; the murmur of aortic regurgitation was attentively sought for in different postures of the body, but we were convinced that no such regurgitation existed. Neither the liver nor spleen was palpable.

These physical signs were confirmed on subsequent occasions.

From February to July the patient was repeatedly examined and special observations made upon him. These are described under succeeding subheadings. The actual dates upon which the observations were made will be stated. The whole series of observations could not be carried through at a few sittings; but there was a sufficient overlap and repetition of the enquiries to show that the circulation during this period was sufficiently constant to justify the different observations being treated as a whole.

Records of the murmur over the femoral vessels were obtained, and one of these is shown in Fig. 27. The murmur is expressed by rapid oscillations (the rate of the main oscillations being about 125 per second), which run continuously throughout the curve and rise in amplitude rhythmically. The rise in amplitude is shown, by a simultaneous pulse record from the left femoral artery at the same level, to begin very shortly after the upstroke of the pulse; the sound vibrations reach their maximal point a little later than the summit of the pulse.

Heart rate.

The heart rate was excessive. While the patient was up, walking quietly or standing, and for some while after he lay down, it ranged between 90 and 110 beats per minute; after he lay quietly for an hour it usually fell to 80 or 85 per minute, sometimes it fell a little lower.

Change on closing the right femoral artery. The effect of this procedure upon heart rate was noticed to be constant at all visits of the patient. It consisted of a fall of rate, of which the following are representative examples.

Pulse rates.

Date.	Femorals open.	Rt. femoral closed.
February 1st ...	103	67
	97	67
	88	63
	91	64
	96	60
February 21st ...	102	80
	88	64
March 3rd ...	72	54
	79	49
	73	50
March 29th ...	83	52
April 6th ...	86	59
June 19th ...	81	52
July 3rd ...	75	46

The fall was conspicuous, amounting to 20 or 30 beats per minute. On one occasion the compression was maintained for periods of several minutes with a view to determining any further change of rate following the initial slowing. The slowing on compression was from an average of 86 down to 58 beats per minute: within a few seconds the rate rose on an average to 61 beats, this slight acceleration being present on each occasion and being completed rapidly. The subsequent rate remained constant during the long compression. Obliteration of the left common femoral artery was always without effect on the heart rate.

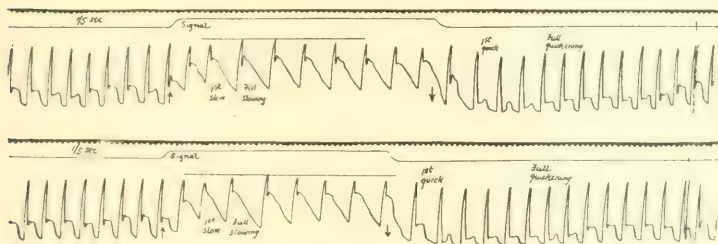


Fig. 1. ($\frac{1}{8}$). Case 1 (March 29th). Two sphygmographic records from the radial artery to show the effects of compressing the right femoral artery.

Many continuous sphygmographic and optical records from the radial artery were taken on different days, the right femoral vessel being compressed or decompressed while the record was running. The response of the heart rate to compression or decompression, these events* being signalled on the same record, was usually shown to have begun with the next heart beat, occasionally by the next beat but one: that is to say, within $\frac{1}{2}$ to 1 second. Full slowing was usually reached within 2 or 3 seconds of compression; full acceleration was usually reached within 5 or 6 seconds of the act of decompression (Fig. 1).

Effect of atropine. On the 6th of March a thirty-third of a grain of atropine was given hypodermically at three minutes past seven o'clock. Soon after the pulse began to quicken, the usual reaction on compressing the femoral artery was found to be much diminished. When the rate had risen to 130 per minute, the reaction was practically abolished. The pulse rate rose no higher than 132 beats per minute and shortly after nine o'clock the rate began to decline. The atropine injection produced dryness of the mouth and wide dilatation of the pupils.

* The signal of compression, or decompression, has been operated by hand in all cases, and is only accurate to one-tenth of a second.

Pulse rate under atropine.

Time.	Femorals open.	Rt. femoral closed.
7.0 1.33 grain atropine		
7.5	84	—
7.10	86	—
7.12 $\frac{1}{2}$	84	—
7.15	84	—
7.17 $\frac{1}{2}$	90	—
7.20	88	—
7.22 $\frac{1}{2}$	92	—
7.25	100	—
7.27 $\frac{1}{2}$	102	—
7.29	106	—
7.30	91	86
7.35	108	86
7.36	97	94
7.38	110	97
7.4 $\frac{1}{2}$	115	101
7.46	107	99
7.48	104	100
8.18	124	118
8.20	122	117
8.26	123	117
8.30	124	112
8.45	132	126
8.47	130	128

The corresponding rates for compression were not obtained while the patient was passing under atropine, but the reaction had been previously noted to be of its usual extent.

Arterial pressure.

On February the 1st the average systolic blood pressure in the right brachial artery was 149 and the diastolic pressure was 55 mm. Hg.. These pressures are comparable to those found in regurgitation from the aorta. On February the 23rd the average systolic and diastolic brachial pressures were 154 and 55 mm. respectively: on this day the systolic pressure in the right popliteal artery measured 129 mm., while that in the left popliteal averaged 188 mm.. Thus, the average systolic pressure in the right popliteal was 25 mm. lower than in the right brachial artery and 59 mm. lower than in the left popliteal. The low pressure in the right popliteal was evidently due to the pulse wave spending much of its energy in the corresponding vein. The large size of the right common femoral pulse would seem to indicate that an attempt to compensate the deficient blood flow to the right leg had occurred, by expansion of the right common femoral vessel.

Effects of femoral occlusion. The following table illustrates the effects of obliterating the common femoral arteries upon brachial blood pressure. The readings were taken alternately by two observers.

Right brachial pressures (alternatively with and without obliteration of a femoral artery).

Observer.	Femoral arteries open.		Rt. femoral closed.		Lf. femoral closed.	
	(syst.)	(diast.)	(syst.)	(diast.)	(syst.)	(diast.)
T. L.	150	55	162	85	—	—
A. N. D.	150	55	165	88	—	—
T. L.	150	55	160	85	—	—
A. N. D.	150	52	—	—	150	58
T. L.	146	58	—	—	150	52
Averages ...	149	55	162	86	150	55

Briefly, on occluding the right common femoral artery, the systolic pressure rose in the average 13 mm. Hg.; the diastolic pressure rose 31 mm. Hg.; the pulse pressure fell 18 mm., namely, from 94 to 76 mm. Hg.. This rise of diastolic pressure and diminution of pulse pressure constituted the chief changes when escape of blood into the vein was prevented, and were the more notable since compression of the right femoral was accompanied in each instance by the usual fall of pulse rate, a change which would tend to reduce the level of the diastolic pressure, and to raise the corresponding systolic readings. Compression of the left femoral artery was without effect. In this table the pressures which became established after closure of the right femoral are given; on subsequent occasions we noted a preliminary rise of systolic pressure to a somewhat higher point: this higher pressure was maintained for a few pulse cycles only. It was reflected in our pulse curves (see Fig. 1), the summit of the 3rd wave following compression almost constantly reaching the highest level. Similarly, on releasing the compression, the 3rd or 4th wave succeeding stood usually at the lowest level, there being subsequently a slight rise in the level of the beats.

Differential arterial pressures and their changes (February the 21st). The average systolic blood pressure in the left popliteal artery on this day was 182 mm. Hg.; that in the left brachial artery averaged 154 mm., being, therefore, 28 mm. lower. This last phenomenon, as Hill has shown, is a usual physical sign in regurgitation from the aorta, and is a usual accompaniment of such arterial physical signs as exist in our patient, namely, water-hammer pulse and capillary pulsation. The following observations were made upon the arterial pressures with the right common femoral compressed to obliteration and uncompressed, alternately.

Observer.	Left popliteal pressure.		Left brachial pressure.			
	Femorals open.	Rt. femoral closed.	Femorals open.		Rt. femoral closed.	
	(syst.)	(syst.)	(syst.)	(diast.)	(syst.)	(diast.)
T. L.	186	196	156	?	158	80
T. L.	—	208	156	55	162	85
T. L.	184	210	150	55	—	—
A. N. D.	180	207	—	—	—	—
A. N. D.	180	210	—	—	—	—
Averages ...	182	206	154	55	160	82

When the right common femoral was compressed and the effects of the arterio-venous aneurism upon the circulation consequently withdrawn temporarily, the systolic pressure in the left popliteal rose by 24 mm. Hg., a greater rise than that found to occur in the brachial, which was but trifling. This rise was maintained: it was not temporary. The important point is that the difference in leg and arm pressures (*Hill's sign*) was not decreased, on the contrary it was increased when the right common femoral was obliterated.

These observations were repeated subsequently, and the readings are given in the following table:—

Observer.	Left popliteal pressure.		Left brachial pressure.			
	Femorals open.	Rt. femoral closed.	Femorals open.		Rt. femoral closed.	
	(syst.)	(syst.)	(syst.)	(diast.)	(syst.)	(diast.)
A. N. D.	158	175 - 154	138	50	152 - 142	76
A. N. D.	158	185 - 160	134	52	158 - 136	70
A. N. D.	156	185 - 160	130	48	145 - 135	68
T. L.	154	170 - 154	136	50	142 - 142	75
T. L.	158	170 - 150	134	50	144 - 134	76
T. L.	140	165 - 146	136	54	150 - 140	80
Averages ...	154	175 - 154	135	51	150 - 138	78
March 29th.						
T. L.	152	172 - 166	152	54	160 - 150	75
T. L.	160	194 - 166	—	—	—	—
A. N. D.	150	180 - 158	152	54	168 - 150	75
Averages ...	154	182 - 163	152	54	164 - 150	75
April 6th.						

On these days it was noticed that on compressing the right femoral artery the pressure in brachial and popliteal rose for a few beats to a high point and fell away again. These high points of systolic pressure were obtained on this and subsequent occasions by raising the pressure in the armlet above the obliteration point with the right femoral open, and noting the forcing of the armlet by the beats on closing the femoral: by rapidly raising the pressure in the armlet for the succeeding beats or by repeating the observation, these high points could be measured with sufficient accuracy. The readings of the first table (February the 21st) do not include these high points, but represent the more stable subsequent pressures.

Reviewing the readings as a whole, it is clear that the difference in arm leg pressures was inconstant in degree. On one occasion there was a conspicuous difference, and on this occasion the difference was increased by closing the right femoral artery: on a second occasion the difference was somewhat less, but was maintained on cutting out the aneurism: on the third occasion the brachial and popliteal pressures were equal, but a difference in pressure developed when the right femoral artery was closed.

Readings under atropine. These readings were taken at the height of the atropine reaction, previously described (March the 6th at 8.30 p.m.), the object being to eliminate the effects of change of pulse rate.

Observer.	Left popliteal pressure.		Left brachial pressure.			
	Femorals open.	Rt. femoral closed.	Femorals open.		Rt. femoral closed.	
	(syst.)	(syst.)	(syst.)	(diast.)	(syst.)	(diast.)
T. L.	158	192-172	142	54	160	95
T. L.	148		146	60	158	96
T. L.	162		140	64	-	-
A. N. D. . . .	150		152	52	156	92
A. N. D. . . .	148	182-175				
A. N. D. . . .	152	182-174				
Averages . . .	153	185-174	145	57	158	94

In the brachial vessel the systolic pressure rose 13 mm. and the diastolic pressure rose 37 mm. on closing the right femoral artery. Thus, the change in pulse pressure was somewhat more conspicuous, though in the same direction, as that found in the unatropinised patient. A small difference between the systolic pressures of popliteal and brachial was found. This difference was materially increased when the right femoral artery was closed, the pressure rising in the popliteal from 153 to 185-174, while it rose in the brachial from 145 to 158 only.

Arterial curves.

The pulse of this patient was of conspicuous water-hammer quality, especially when the arm was raised to the vertical position. Corresponding changes were expected, and were found, in the rapidity of the pulse's measured upstroke. Many optical pulse curves were taken from the right

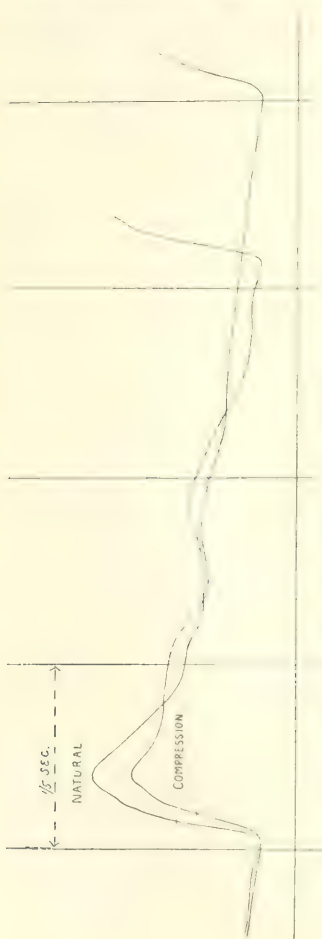


Fig. 2. Case 1 (February the 1st). The superimposed outlines of two optical records of the pulse. Arm horizontal. The curves show the changes occurring in the pulse on compressing the right femoral artery.

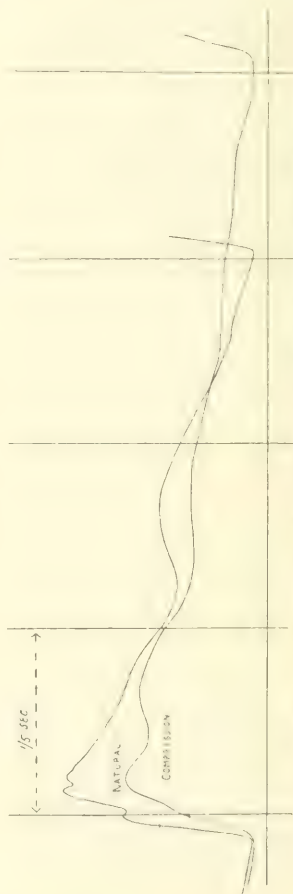


Fig. 3. Case 1 (February the 21st). Similar outlines to those of Fig. 2. Arm vertical.

radial artery. The upstroke of the pulse was seen to be unusually abrupt in its initial phases: the summit was prominent and the fall to the dirotic steeper than normal. The first feature was exaggerated by raising the arm to the vertical position, and in this position a thrill was recorded at the summit of the curve. On February the 1st, the arm being horizontal, the interval between the beginning of the upstroke and the summit of the pulse wave measured 0.066 of a second: the half-way point of the upstroke was reached in 0.019 of a second. Both these values are less, the latter notably less, than those found for normal pulses. On February the 21st these observations were repeated and the values 0.060 and 0.026 were obtained: immediately afterwards the arm was raised to the vertical position, without moving the receiver, and the corresponding curves now gave average readings of 0.068 and 0.015 of a second. Thus, the rate at which the upstroke was written increased considerably in its initial phases when the arm was raised. In brief, the form of the pulse curve was similar in all respects to that commonly manifested by cases of free aortic regurgitation and presented a similar change to that which is seen in this disease on raising the arm.

Effect of closing the right femoral artery. The abnormalities of the pulse form are most clearly to be appreciated in this patient from a comparison of the curves taken with the femoral artery open and closed. Examples of such curves, taken with the arm horizontal and within a few seconds of each other, are shown in Figs. 17 and 18: two curves showing very similar features have been enlarged and superimposed in Fig. 2. The pulse became slower and its amplitude decreased when the femoral artery was closed: simultaneously the interval in which the initial phase of the upstroke was inscribed (the half-way points are marked in Fig. 2) increased: the pulse became more sustained, being followed by a prominent predirotic wave almost equalling that of the primary wave in height, thus producing a form of plateau: the summit of the pulse became a little delayed. These changes were constant, though varying slightly in their degree, in all the observations undertaken. The features to which we draw especial attention are as follows. The rates at which the first half of the upstroke was inscribed became slower, a slowing which was both absolute and relative. Naturally, the inclination of the upstroke was influenced by its decreased amplitude, but that was not the complete explanation of slowing, the half-way point being reached after a distinctly longer interval. Closure of the right femoral artery prolonged the intervals from 0.065 and 0.019 to 0.072 and 0.026 (February the 1st), and from 0.060 and 0.026 to 0.063 and 0.029 (February the 21st). Simultaneously, the element of collapse, between the summit of the pulse and the dirotic notch, was abolished.

Change in the rapidity of the upstroke was shown even more conspicuously by curves taken with the arm held vertically. While the femoral artery was patent the summit was reached in 0.068 and the half way point in 0.015 of a second; on closing the femoral vessel these values altered to

0.074 and 0.023 of a second. The difference in the rate of upstroke is well displayed in the superimposed curves of Fig. 3. The natural curve of this figure presents on its upstroke and summit three small waves, the waves responsible for the palpable thrilling quality of the pulse when the arm was held aloft. These secondary waves disappeared when the femoral vessel was compressed.

Obliteration of the left femoral artery, undertaken as a control, had no noticeable effect upon the pulse form.

The changes produced in the character of the pulse by closure of the right femoral artery may be summed up by stating that those features of the pulse, in which it originally resembled the pulse of aortic regurgitation, were abolished.* Strictly speaking, this is perhaps not entirely true of the water hammer quality (quick upstroke), for the values obtained on closing the femoral artery were still those on the very lowest limits of normality. This tendency for abruptness to persist will be discussed subsequently.

That the chief changes in the pulse form described were due exclusively to the stopping of the leak from arterial to venous system, and not to change in filling of the heart or to altered heart rate, was shown conclusively by the following observations. The change in form occurred almost immediately the femoral was closed. It was shown in some degree or conspicuously by the pulse beat directly following compression (Fig. 22); it was displayed completely by the succeeding pulse beat or pulse beat but one. That it should not always display itself completely by the pulse beat directly following compression is but natural, in that the leak would be prevented only in part of the preceding cycle. The change in form often occurred before the pulse had changed materially in rate (Fig. 22). Similar abrupt changes of form were seen to follow immediately upon the opening of the femoral artery (Fig. 23).

Lastly, we abolished the rate factor by administering atropine and similar changes of pulse form were still observed. A pair of curves taken within a few seconds of each other while the patient was under atropine is illustrated by Figs. 19 and 20: in these the arm was horizontal. A similar pair, taken with the arm vertical, is illustrated in Figs. 21 and 22. The second curve of each of these pairs was taken with the right femoral artery closed. The essential and previously described changes of form on closing the right femoral artery, are again displayed. A beat from each of the two curves 19 and 20 has been enlarged, and the two superimposed in Fig. 4. The pulse rates are almost identical: the lessened amplitude, the slower upstroke, the delay and broadening of the summit, are all clearly shown. In this figure the dicrotic notch comes earlier, and the dicrotic wave is earlier and less prominent, in the curve corresponding to closure of the femoral artery.

* Here it is to be noted, however, that the leak occurred in systole as well as in diastole, in which respect it differs from that found in aortic regurgitation.



FIG. 4. Case 1 (March the 6th). Similar outlines to those of Fig. 2. Taken while the patient was almost fully under the influence of atropine. The natural curve and that taken during compression have been drawn as unbroken lines; the amplitudes of the last curve have been proportionately raised and the curve re-drawn as a dotted line also, so that it may be the more easily compared with the natural curve from this patient.

Measurements of upbeat initial curves.

Date.	Pulse rates.	Begin. of stroke to half-way pt. in secs.	Begin. of stroke to summit in secs.	Femoral arteries.	Arm.
Feb. 1st.	104	0.019*	0.065*	Open.	Horizontal.
	67	0.020	0.072	Rt. closed.	"
	97	0.027	0.071	Open.	"
	67	0.027	0.071	Rt. closed.	"
Feb. 21st.	91	0.021	0.068	Open.	"
	92	0.022	0.071	Li. closed.	"
	102	0.026	0.060	Open.	Horizontal.
	64	0.029	0.063	Rt. closed.	"
Feb. 21st.	88	0.014	0.071	Open.	Vertical.
	72	0.025	0.074	Rt. closed.	"
	85	0.017	0.066	Open.	"
	64	0.021	0.074	Rt. closed.	"
March 6th, under atropine.	115	0.017	0.070	Open.	Vertical.
	101	0.028	0.083	Rt. closed.	"
	124	0.018	0.059	Open.	"
	118	0.030	0.060	Rt. closed.	"
	123	0.025	0.007	Open.	Horizontal.
	117	0.029	0.076	Rt. closed.	"

* Error of measurement calculated for these measurements at approximately 0.002-0.003 of a second.

The dotted outline corresponds to the curve taken with the femoral artery obliterated; the ordinates have been raised in value proportionately throughout to bring the summits of the compared curves to the same level. The essential differences in the forms of the two curves is more clearly displayed by this procedure.

The immediate, or almost immediate, change in form, on compressing or releasing the right femoral artery, while the patient was under atropine and the heart rate practically constant, is illustrated by Figs. 24 and 25.

Capillary pulsation.

This patient presented, both while standing and lying, a spontaneous "capillary pulsation" in the skin of the forehead and cheeks with each heart beat. The lips were of good colour and this colour showed no pulsation until the lip was pressed with a sheet of glass. A vivid change of colour from red to pale pink appeared in this circumstance. The degree of this pulsation in the lip was as great as any we have witnessed in free aortic regurgitation. Slight pulsation was seen in the nails when these were pressed upon, but not otherwise. The pulsatile flushing of the skin of the face and of the lips was not diminished when the right common femoral artery was closed, and all pulsation and thrill in the artery and tumour below was abolished. These observations were repeatedly witnessed by all the workers in the laboratory and demonstrated at the March meeting of the Physiological Society. They were repeated on March the 6th while the patient was under the full influence of atropine with precisely similar results; the persistence of the capillary pulsation was thus shown to be unconnected with the usual change of heart rate. During the observations under atropine and before the closure of the femoral artery a certain grade of pressure on the lip procured a vivid red to white pulsation. If this pressure were maintained and the femoral artery was then closed, the colour deepened during the diastolic phase, but the vivid red to white pulsation was at once restored in its full intensity by exerting slightly greater pressure on the lip. Evidently the white or light pink colour of diastole is due to collapse of the vessels under pressure and the red flush to their refilling; the vessels collapsed more readily when diastolic pressure was low (femoral artery open) than when it was higher (femoral artery closed).

Venous pressures.

The calf of the right leg appeared to be a little larger than that of the left and proved so on measurement. Just below the knee the circumference of the left leg was 29 cm., and of the right leg 29.75 cm.. The maximal circumference of the left calf was 32 cm., and of the right calf 33.5 cm.. The veins of the right leg were somewhat more conspicuous, and felt as if under greater pressure. Maintaining the patient in a horizontal position and bringing all veins from which readings were to be taken to the same level, the following measurements were obtained on different days.

Venous pressures in cm. of water (Hooker's method).

Date.	Sternum to vein in cm.	Observer.	Dorsal vein of hand.	Internal maleolar.		
				Left.	Right.	
March 6th ...	13.5	—	13.2	—	—	Average value.
		—	0.3	—	—	Corrected average.*
March 29th ...	17	A. N. D.	17	20	21	
		T. L.	16	20	21	
		T. L.	15	20	21	
		T. L.	—	18	—	
		T. L.	—	17	—	
		A. N. D.	—	16	26	
		A. N. D.	—	19	26	
		A. N. D.	—	21	28	
			—	20	—	
			16	19.0	23.8	Average values.
			1.0	2.0	6.8	Corrected averages.*
April 6th ...	13.5	—	13.0†	—	—	Average value.
		—	0.5	—	—	Corrected value.*

* Corrected to level of sternum.

† This value was controlled by a direct reading (Moritz method) from the left basilic vein and proved accurate within $\frac{1}{2}$ —1 cm.

In this table the readings for the several days are averaged, and corrected averages are given in heavy type. These corrected averages express the pressure relative to the level of the sternum in cm. of water. In the readings from the hand there is uniformity, the pressures being represented by a column of water falling short of the level of the sternum by 0.3 to 1.0 cm.. The pressures in the right maleolar vein were greater than these by about 8.0 cm. water.

Effect of closing the right femoral artery. On March the 6th the pressure in a dorsal vein of the left hand was estimated before and after closing the right femoral artery, and we then believed that we were able to observe a distinct fall of pressure when the arterio-venous aneurism was cut out. In attempting to demonstrate this fall of venous pressure on a subsequent occasion to a meeting of the Physiological Society we failed; and now believe our first observation to have been for some reason erroneous. Reading the venous pressure repeatedly with right femoral open or closed, on two further occasions, we were unable to convince ourselves of any distinct change on closing or releasing the right femoral artery. If the right femoral artery were closed and opened under cover by one observer, while the second observer obtained readings of the venous pressure in the hand, these readings

failed to determine the state of the right femoral artery. These later observations, failing as they did to confirm our first ones, left us in doubt as to the precise effects of stopping the leak into the veins. To decide the question we introduced a wide bore needle into the left basilic vein in the direction of the blood stream, this needle being connected to a manometer of saline solution containing 0.5 per cent. of sodium citrate. The vein at the point of puncture lay 14.5 cm. below the sternum and the column of saline became steady near the level of the sternum, the meniscus oscillating with respiration through approximately a half centimetre, and continuing to do so throughout the observations. The following readings* were obtained :—

Basilic vein pressures in cm. water (direct method).

	Femorals open.	Rt. fem. closed.	Lt. fem. closed.
	15.0	15.5	—
	15.0	15.4	—
	15.0	15.4	—
	15.0	—	15.5
	15.0	15.3	—
	15.0	—	15.7
	15.5	15.7	—
	15.1	15.5	—
Average values	15.07	15.46	15.6
Corrected values	0.57	+ 0.96	+ 1.1

These observations were decisive : at each compression of the right femoral artery, a slight but distinct rise of the meniscus occurred, amounting in the average to 0.4 cm. of water. A similar rise was seen on occluding the left femoral artery : closure of the right brachial artery was without any apparent effect. The change which occurred was in a direction contrary to that originally anticipated. The rise of pressure was trifling in amount and was obtained equally by closure of either femoral artery. The rise and fall of the meniscus on closing and opening the artery occurred constantly after a delay of several seconds. The rise on compression was maintained so long as the femoral artery was closed, the compression being sometimes continued for 15 or 20 seconds.

The actual cause of the slight rise is not known definitely ; very probably the pressure upon one or other femoral vessels induced a little increase in the abdominal muscle tone ; such could not, in point of fact, be detected. It is clear, however, since both arteries gave similar effects, that cutting out the leak from artery to vein induced no measurable change of venous pressure.

* For simplicity the higher of these readings is alone used in the table.

Size of heart.

Two orthodiagrams of the heart were taken on the same day. These two outlines were in almost absolute agreement. The transverse diameters of the heart averaged 13.6 cm. and the longitudinal 14.0 cm. (the generally accepted maximal normal measurements of a man of this weight are 11.3 and 13.5 cm.; Claytor and Merrill¹). One of these orthodiagrams is shown in Fig. 5.

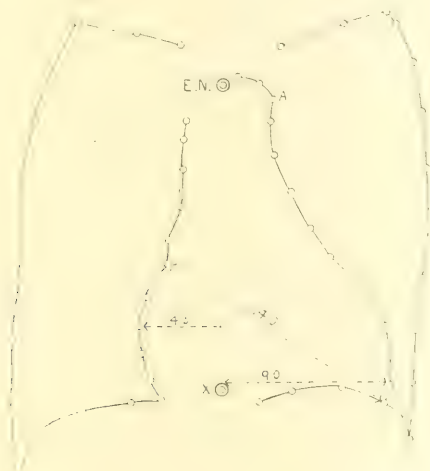


Fig. 5. ($\times \frac{1}{2}$). *Case 1* (February 21st). One of a pair of similar orthodiagrams taken to ascertain the precise size of the heart, viewed artero-posteriorly. Patient sitting; breath held in slight inspiration. E.N. = episternal notch. X = xiphisternum.

Change in size of heart. The patient stood before the orthodiagraph and the outline of the heart was mapped. The femoral artery was then compressed and, during compression the outline of the right auricle was recorded again. The new outline fell a half centimetre inside the old one. This observation was repeated several times. In two of the four observations the auricular contour during compression fell a half centimetre within the ordinary contour, in the remaining two the contours fell together. These results lacking consistency, the patient was placed behind a large fluorescent screen, and the body held rigidly against the screen. A line was drawn upon

the screen along the edge of the right auricular shadow, and the right femoral artery was repeatedly compressed and relaxed, the relation of the shadow to the line on the screen being observed. Working in this fashion the auricular contour appeared to occupy a constant position during diastole, whether the femoral artery was compressed or not, and it became displaced inwards and flattened out a little in systole: this movement was decidedly greater when the femoral artery was compressed, the difference being about a half centimetre. Thus, it would seem that the average size of the auricle diminished when the femoral was obliterated. Observations upon the left contour of the heart failed to show any appreciable change in its position during compression of the femoral artery.

Change in heart sounds.

On compressing the right femoral artery the sounds at the cardiac impulse remained unaltered: at the aortic cartilage the second heart sound was intensified by the same procedure, an observation made independently by three observers.

Changes in the electrocardiogram.

Two series of electrocardiograms were taken from leads *I*, *II* and *III*, the patient lying: the one series while the right femoral artery was compressed, the other while the artery was patent. The changes are averaged in the accompanying table: they are but slight and are for the most part similar in direction and degree to those seen when the heart rate changes spontaneously.

	Lead <i>I</i> .		Lead <i>II</i> .		Lead <i>III</i> .	
	Fem. open.	Fem. closed.	Fem. open.	Fem. closed.	Fem. open.	Fem. closed.
Heart rate	72.0	54.0	79.0	49.0	73.0	50.0
<i>P</i>	1.0	1.0	2.0	1.0	1.0	0.0
<i>Q</i>	0.5	0.5	3.0	2.0	2.5	1.5
<i>R</i>	14.0	13.5	24.0	25.5	13.9	13.0
<i>S</i>	1.5	1.0	1.5	1.5	1.5	1.5
<i>T</i>	3.5	3.5	4.0	6.0	3.0	2.5

Velocity of pulse wave and its changes.

On April the 20th optical records were taken from the right radial artery simultaneously with an electrocardiogram from lead *II*. The record was taken before and during occlusion of the right femoral artery. A similar

series of curves was then taken from the right subclavian artery. In the following table the intervals between the summits of *R* and the corresponding pulse upstrokes are given. Each of these values is an average of three readings. On closing the femoral artery the interval *R* to radial was practically unaltered; but the interval *R* to subclavian increased by 0.023 of a second: the interval subclavian to radial decreased by an average value of 0.028 of a second. The pulse wave velocities were 754 and 1,150 mm. per second with the femoral artery open and closed, respectively. This rise in velocity we attribute to the considerable increase of diastolic pressure

Pulse wave intervals.

Pulse rate.		<i>R</i> to subclavian.		<i>R</i> to radial.		
Fem. open.	Fem. closed.	Fem. open.	Fem. closed.	Fem. open.	Fem. closed.	
82	60	—	—	0.136	0.131	
80	53	0.052	0.079	—	—	
80	51	0.058	0.076	—	—	
—	50	—	0.079	—	—	
Averages	81	53	0.055	0.078	0.136	0.131

occurring in our patient on occluding the femoral artery. Such changes of velocity with increased arterial tension have recently been described by Bramwell and Hill², who worked upon a schema; our patient has presented an unusual opportunity of testing the effect of altered diastolic pressure on pulse wave velocity in the human subject. There was, of course, in our patient a simultaneous change of pulse rate and a change in the character of the pulse's upstroke, factors which we regard as insufficient to produce the altered velocity found.

Seeing that the pulse wave was conducted more rapidly when the femoral was compressed, its increased delay in reaching the subclavian in similar circumstances can only be attributed to an increase in the pre-sphygmie interval. This increase appears to have amounted to approximately 0.023 of a second.

Size of capillaries and the capillary flow, and their changes.

A slight but perceptible deepening in the colour of the face was seen on closing the right femoral artery. Viewing the capillaries of the finger nail bed under a 2,3 objective (Lombard's method) on April the 20th the stream of blood in the capillaries was seen to be sluggish. On compressing the right femoral artery, the capillaries invariably became fuller after a short delay and the blood flow through them was appreciably quickened. These changes were unmistakable, being witnessed repeatedly by a number of observers.

Volume of the unaffected limbs and its change.

The right arm was enclosed in a plethysmograph containing water* at body temperature and extending a little way above the elbow, or the left leg in one which extended almost to the knee. The plethysmograph was sealed off proximally and connected by tubing to a volume recorder. The effect of occluding the right femoral artery upon the volume of the two limbs was tested repeatedly on a number of occasions and gave almost constant results. The arm displaced 1,795 cc. of water and this volume was increased by approximately 1 or 2 cc. on cutting out the aneurism: the rise of the curve began immediately (Fig. 6) and was sometimes shortly followed by a second rise of different origin and of about similar amount (see Fig. 9). The first rise of volume was anticipated, for compression of the right femoral was already known to increase mean arterial pressure and to

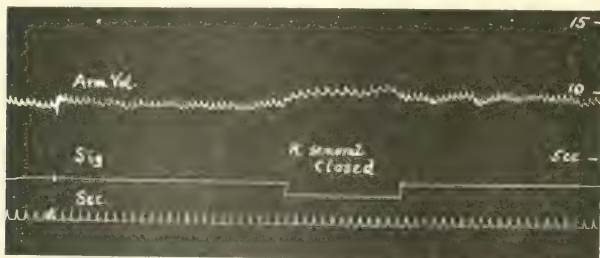


Fig. 6. Case 1 (June the 5th). Volume curve of right arm and signal of closure of right femoral artery; the time is in seconds in this and similar records.

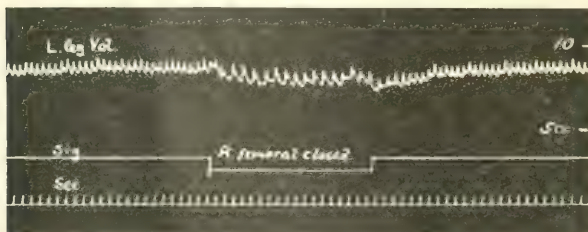


Fig. 7. Case 1 (June the 5th). Volume curve of left leg and the effect upon it of closing the right femoral artery.

* On a subsequent occasion we used air and obtained similar results. Observations on the leg were made with the patient supine, those on the arm were made with the patient in a similar posture, or sitting with the elbow bent at a right angle.

distend the capillaries a little. That it was purely arterial in origin is shown by its being unaffected if the venous pressure in the limb were previously raised and maintained constant by compressing the arm above the plethysmograph with a pneumatic armlet at 25 or 40 mm. Hg. The increase of arterial volume is attributed to an increase of mean arterial pressure immediately consequent on the closure of the right femoral vessel and cannot be assigned to an increased output from the heart, for the rise always occurred without delay. The second rise of volume when present occurred after a delay of about 10 or 12 seconds (Fig. 9), and is probably attributable to the slight rise of pressure in the veins of the limb already noted as occurring: for it appeared whether occlusion of the right femoral artery was sustained, or if the latter was released previous to its occurrence. This second rise was not constant, however. At more than one sitting we saw no sign of it. Compression of the left femoral artery had no measurable effect on the volume of the left arm.

The volume of the left leg (2,680 cc.) was not increased on compressing the right femoral artery; on the contrary, the leg decreased in size by approximately 1 or 2 cc. (Fig. 7). This difference in the behaviour of the leg is of interest. As in the case of the arm, so in the case of the leg, closure of the right femoral would increase mean arterial pressure. In so far, therefore, as the arteries are concerned, change in them would tend to increase the volume of both limbs: constancy of volume or diminution of size can only be accounted for by supposing a decrease in the volume of the leg veins. This seems to us a reasonable explanation in the case of the left leg. The arterio-venous anastomosis was in the upper part of the right thigh, its opening lying but a few inches from the mouth of the left common iliac vein. It is to be supposed that with the anastomosis open the zone of increased venous pressure extended at least as far as the mouth of this vessel, thereby slightly raising the venous pressure in the left leg: if that were the case, the venous pressure would fall a little in the left leg and its volume would tend to decrease on closing the right femoral artery. The diminished out-flow from the right leg below the aneurism, in part following from the arterial obstruction and in part possibly from simultaneous occlusion of the femoral vein, would tend in the same direction. The only objection to this view has been our inability to detect a fall of venous pressure in the left leg by Hooker's method: the method, however, is insufficiently delicate to detect minor changes of pressure with certainty.

So far as volume change on closing the aneurism is concerned, our evidence points to permanent retention of a small extra amount of blood in the arteries: this gain of blood by the arterial system must, of course, have been balanced by a loss of blood to the venous system. Since the general venous pressure was not lowered, it is to be supposed that this loss to the venous volume occurred in the veins of the left leg, in the venous aneurismal sac, and in small part in the arteries of the right leg and probably the veins of this leg also.

In the case of the arm, which was small, we used a circular pneumatic cuff of 5 cm. breadth and a pressure of 48 mm. Hg. suddenly applied.* in the case of the thigh we used a special cuff having a breadth of 15 cm. and a pressure of 38 or 40 mm. Hg.. The amount of blood flowing into the limb in a given space of time is subsequently ascertained by calibrating the instrument in cubic centimetres.† Repeated observations on arm, or leg, or both, were made on four occasions and gave satisfactorily uniform results so far as both limbs were concerned. A comparison was instituted between the inflow into these limbs with the right femoral artery open and closed. Fig. 8 shows the effect on the right arm volume of suddenly impeding the venous return with the anastomosis open. The volume begins to increase at an almost uniform rate immediately the cuff pressure is raised and continues to do so until the recording drum is stopped. The volume increase is 5 cc. in 41 seconds. Fig. 9 first shows the effect on arm volume of closing the right femoral artery. There is an immediate rise (a) of 1 cc. in volume followed by a second rise after a delay of about 10 seconds. The curve then runs level until the venous return in the arm is suddenly obstructed. At this obstruction the volume immediately begins to rise (c) and the curve is continued steeply until the drum is stopped and the pressure in the cuff lowered. The rate of volume increase over the first stretch of this curve is 5 cc. in 15.5 seconds. Similar volume curves, taken from the left leg, are illustrated by Figs. 10 and 11.

The accompanying table serves further to illustrate the time in seconds taken for the first 5 cubic centimetres of blood to flow into the corresponding limb. These curves of volume change were taken on June the 5th and July the 3rd, alternately with the right femoral open and closed; they are sufficiently representative of the whole series of observations.

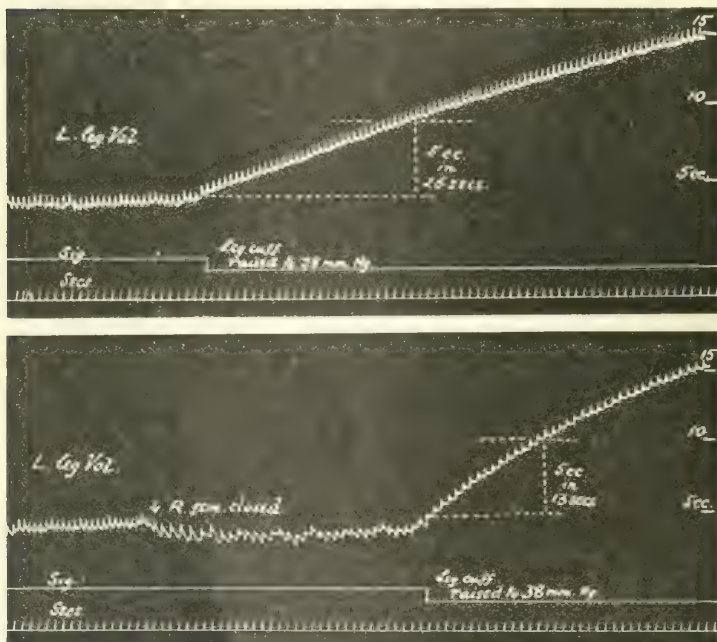
Rate of blood flow to limbs.

	<i>Right arm.</i> (Volume 1,795 cc.).		<i>Left leg.</i> (Volume 2,680 cc.).	
	Femorals open.	Rt. femoral closed.	Femorals open.	Rt. femoral closed.
June 5th	41	15.5	26	13
	37	16	26	13
	45	14	25	17.5
	—	16	—	—
Averages in secs. ...	41	15.4	26	14.5
July 3rd	17	8
	18.5	8.3
	23	11
Averages in secs.	19.5	9.1

* Such pressure being chosen as would not affect the size of the artery in diastole.

† The initial stage of the rise of volume being alone used for the purpose, because it corresponds to the period when the pressure in the veins is lowest.

The inflow to the right arm with the right femoral artery closed averages 5 cc. in 15.4 seconds, or approximately 20 cc. per minute; the inflow per 100 cc. of limb per minute was therefore 1.1 cc. per minute. This value is lower than that given for normal subjects by Hewlett.



Figs. 10 and 11. Case 1 (June the 5th). A similar pair of curves (slightly reduced) taken from the left leg, and comparing the inflow of blood to this limb with the right femoral artery open and closed.

The inflow per 100 cc. of the left leg, with the right femoral closed, was a little less, amounting to just under 1 cc. per 100 cc. of tissue per minute on June the 5th, and rather more than this on July the 3rd.

Our observations were undertaken particularly to compare the inflow with the right femoral artery closed and open, and we have consistently found the flow to be greatly increased by closing this artery and thus cutting out the anastomosis, an observation which is entirely compatible with the

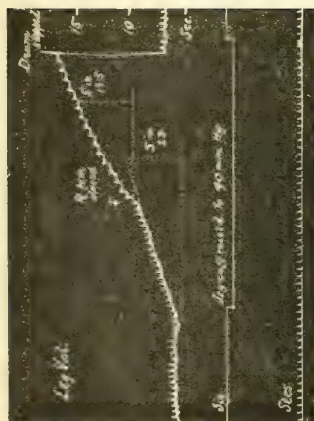


Fig. 12. Case 1 (July the 3rd). Volume curve ($\times 4$) showing the immediate increase in the rate of flow into the left leg when the right femoral artery is closed.

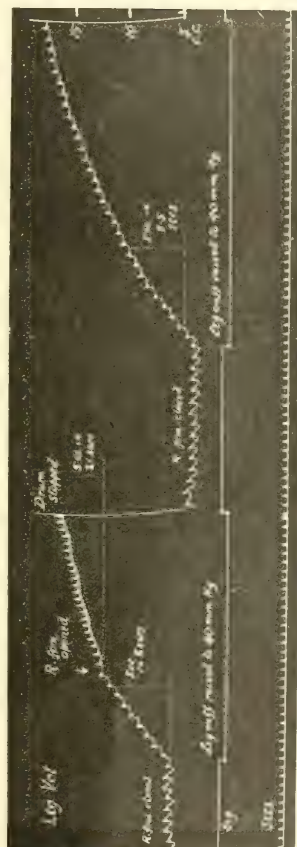


Fig. 13. Case 1 (July the 3rd). Volume curve ($\times 1$) of left leg. The first curve shows the immediate decrease in the rate of inflow into the limb on opening the right femoral artery. The second curve is a control showing the rate of inflow into the limb with the arterio-venous aneurism closed throughout.

increased velocity of flow observed in the capillaries.* Briefly, these show that compression of the right femoral artery increased the blood flow to both the left arm and left leg by approximately 100 per cent.; and there is no obvious reason why this measure may not be taken as an index for the tissues of the body in general. If it is assumed that the output of the heart remained constant while the aneurismal connection was free or closed, then the conclusion may be carried further; for we must in that case allow that, while the aneurism was open, half the heart's output passed through the aneurismal sac. Such a conclusion does not appear to us to be inherently improbable, since the superficial femoral artery is naturally large, and since autopsies and experimental work have shown it frequently much dilated on the proximal side of an arterio-venous communication. The more forcible pulse in the right, as opposed to the left, common femoral artery in our patient is consistent with dilatation of the former vessel in our own patient. Moreover, it is to be remembered that the blood flowed through the communication against a resistance which was almost inappreciable, amounting, at the most, to about 7 cm. of water (right maleolar vein pressure) when our patient was lying horizontally: the flow from the artery to the vein must have been very similar in amount to that which would be attained were the aperture in direct communication with the atmosphere. The assumption remains that the output of the heart was the same whether the communication is open or closed. For this there is evidence. We know that in these two circumstances the venous pressure remained practically unaltered: from this we may conclude that the input to the heart remained practically constant. It is true that in our observations we have witnessed a trifling rise of venous pressure on closing the right femoral artery, and it is conceivable that this rise of pressure might in small measure increase the cardiac output; but the increased flow to the sound limb, when the arterio-venous communication was stopped, cannot be ascribed to this cause. Any increase in output from this source would occur after an appreciable delay, while the pressure change was transmitted from the veins to right heart and while the increased volume of blood was passed from the right to the left side of the heart. The slight rise in the cephalic venous pressure observed was itself a delayed effect. The rise in the amount of blood flowing to the sound limb on compressing the right femoral artery was not a delayed effect, it was immediate, as

* The relatively small amount of blood registered as flowing into the limbs, seemed to us to be perhaps in part attributable to the pressure of water on the limb in the plethysmograph. We, therefore, repeated our observations, using the plethysmographs filled with air (like the water, at body temperature) but obtained similar readings. It is possible that observations upon different patients are not very strictly comparable, since the plethysmograph cannot be rendered air-tight without compressing the limb a little and thus raising venous pressure in it. Such a rise of venous pressure would tend to slow the flow into the limb. We lay chief stress on the comparative readings obtained from our case, namely, before and during compression of the right femoral artery; for the conditions of the plethysmograph in these two circumstances remained constant. That the actual quantities measured by us are not far from true values, however, is indicated by the relative straightness of the lines drawn as the curves ascend. That the blood flow to the limbs in our patient was not a free one was also indicated by the usual coldness of his extremities.

the following experiment, often repeated on both arm and leg, clearly shows. A curve of leg volume is taken and the pressure in a cuff above the plethysmograph is abruptly raised; the rise of volume, described already, immediately begins. When this curve has been recording for a suitable period of time the right femoral artery is closed; the increase in the volume of the leg is at once accelerated; the remainder of the curve presents a uniform sweep throughout its course (Fig. 12). It is similar in inclination and form to the last half of an inflow curve from the same patient when the right femoral artery has been closed previous to the occlusion of the veins (Fig. 13, second curve). Thus, it is clear that closure of the anastomosis at once increased the flow of blood to the limb to its full, and that this flow was maintained at a uniform level.*

The reverse of the observations just described is illustrated by the first curve of Fig. 13. In this, the femoral artery was first closed and, during the period of closure, the veins were suddenly obstructed; the usual steep rise follows and continues until the femoral artery is released. The inclination of the curve at once declines in obliquity, the rate of inflow being reduced to that of the first part of Fig. 12. The first curve of Fig. 13 is followed by a second in which the simple rise of volume caused by obstructing the veins with the right femoral artery closed is shown. The inclination of this curve may be suitably compared with that of the preceding curve of the same figure and with that of Fig. 12. It is to be noted that in the first curve of Fig. 13 there is no second and delayed change in the rate of flow, such as would be anticipated in a case of arterio-venous aneurism in which the opening of the aneurism raised venous pressure.

Thus, we are again brought to the conclusion, for this patient, that neither opening nor closing the anastomosis had any appreciable influence on cardiac output.

That the change in flow to the sound limb was not influenced in an appreciable degree by the cutting off of the arterial flow to the right limb *below* the aneurism has been shown by measuring the inflow to the left arm when the corresponding artery of the left leg was occluded. Between these inflow curves and those taken with both femoral vessels patent we have been unable to detect a difference.

To sum up, it seems to be an unavoidable conclusion that the sole change of importance occurring in the circulation of the blood on closing the arterio-venous aneurism was that the portion of blood, hitherto passing through the aneurism directly to the vein, was now directed to the capillaries, and through these reached the veins; and that by this mechanism the filling of the veins and the output of the heart were maintained at what was practically a constant point. If we conclude, as we must from our data,

* It is probable from these observations that the slight rises of venous pressure, seen on the one occasion when they were examined, on compressing the femoral artery, was actually an inconstant affair, as was the secondary increase of limb volume (Fig. 9b); and that it was absent on most of the occasions on which the flow to the limbs was estimated.

that the blood flow to the tissues of the body generally was not greater than normal when the arterio-venous aneurism of our patient was closed, then our chief conclusion in respect of the circulation in this patient, while the communication was open, namely, that the blood flow to the tissues of the body as a whole was reduced to a half its normal quantity, becomes established.

Observations by Dr. C. H. Kellaway on the carbon dioxide in the alveolar air, its output, and change.

To estimate the CO_2 in the alveolar air, Haldane's method was used and separate estimates were made on three separate days. Inspiratory and expiratory samples were collected with the right femoral artery open and closed: the estimates of CO_2 in these samples are given in the accompanying table. The observations are given in the order in which they were obtained on each day and without omission. The patient was at rest in the sitting posture throughout each series. On the first two days the samples were collected about 4 hours after the evening meal. On the last day they were collected about $1\frac{1}{2}$ hours after the same meal, and these values for CO_2 consequently tend to decline as they are followed down the columns.

It will be seen that on all three occasions the mean percentage of CO_2 in the alveolar air was increased by approximately 0.3 to 0.5 with considerable constancy, providing that the right femoral artery was closed for a time sufficient to permit the new unmixed venous blood to reach the lungs, namely, 30 seconds. One sample, drawn immediately after closure of the right femoral artery, presented no change.

Alveolar CO_2 with right femoral open and closed.

Date.	Alveolar CO_2		Mean percentage.	CO ₂ tension		Diff.	Rt. femoral artery.
	expir.	inspir.		in mm. Hg.	n.t.p.		
May 22nd. 4 hours after food.	5.99	5.37	5.78	41.2		2.6	Open.
	6.27	5.93	6.15	43.8			Closed for 30 secs.*
	5.96	5.32	5.64	40.2		2.6	Open.
	6.19	5.83	6.01	42.8			Closed for 30 secs.*
May 26th. 4 hours after food.	5.59	5.35	5.47	39.0		1.9	Open.
	5.97	5.57	5.74	40.9			Closed for 30 secs.*
	5.65	5.23	5.49	39.1		2.2	Open.
	5.95	5.66	5.80	41.3			Closed for 30 secs.*
June 12th. Beginning $1\frac{1}{2}$ hrs. after food.	6.11	5.92	6.02	42.9		—	Open.
	6.05	5.79	5.92	42.2			Immediately after closure.
	6.09	5.86	5.97	42.6		3.6	Open.
	6.55	6.41	6.48	46.2			Closed for 30 secs.
	5.89	5.64	5.77	41.1		4.9	Open.
	6.47	5.15	6.31	45.0			Closed for 30 secs.
	6.15	5.88	6.02	42.9		—	Closed for 2 mins.
	5.80	5.78	5.79	41.3			Open.
	6.15	5.78	5.96	42.6		2.5	Closed for 2 mins.
	6.15	6.15	6.15	43.8			Closed for 30 secs.

* The intervals marked with asterisks in the last column are approximate.

Two samples, each drawn 2 minutes after closure of the artery, showed a change in the usual direction, but the degree of change was not so conspicuous; these two observations are insufficiently numerous safely to be discussed.

The increased quantity of CO_2 , constantly found in the alveolar air after obstruction of the right femoral artery, is to be regarded as the more normal value in this patient; the lessened percentage found with the artery open is naturally attributed to the passage of arterial blood directly from artery to vein, and forms clear evidence of a free communication between the two vessels. The closure of the right femoral artery, producing as it did this considerable rise of CO_2 tension in the alveolar air, might be expected to change notably the rate or depth of breathing; actually such a change was not witnessed. On each of the first two days of observation the expired air was collected in a Douglas bag for a period of 5 minutes, after the patient had rested quietly for an hour, the right femoral artery being either open or closed throughout the period.

Date.	No. of respirations.	Total ventilation in litres.	CO_2 per cent.	CO_2 output in cc. per minute (dry at n.t.p.).	Rt. femoral artery.
May 22nd.	—	29.45	4.12	222	Open.
	—	31.01	4.23	240	Closed.
May 26th.	54	29.74	3.78	209	Open.
	67	32.71	3.78	229	Closed.

The increased ventilation, shown by the accompanying values, is slight.* The absence of a larger change may be accounted for if it is supposed that when the right femoral artery was closed the arterial blood, though containing a higher tension of CO_2 , reached the respiratory centre in much larger quantity, for an increased supply of blood to the centre would increase the amount of CO_2 passing from its cells to the blood and would thus tend to lower the tension of CO_2 in the respiratory centre. Such a conclusion is in harmony with the remaining observations upon this patient.

* Curves of respiration taken on July 3rd, for successive periods of about 1 minute with the right femoral artery open and closed, showed no constant or material change in respiratory rate or excursion.

CASE II.

The following case, closely resembling the first, has been investigated somewhat less fully, but in many respects confirms the observations already recorded.

H. W., a machine hand, of 26 years of age, first came under observation on June the 6th, 1921.

He joined the army in 1915, a perfectly fit youth of 19 years; after completing his training he was sent to France in 1916, and three months later he was wounded in the neck by a spent bullet; this was removed, and six weeks later he returned to the firing line, and in 1917 was shot in the left thigh. After being in hospital for several months he was discharged from the army. At first his left leg was swollen, but this soon became normal again, and gave place to an aching sensation of the limb when walking. This improved, and he complained only of slight pain in the left leg, and breathlessness and palpitation even at rest, symptoms which have improved since.

March the 28th, 1923. Physical signs. The patient, who was occupied in odd light work, was 5 feet 1 inch in height, and 114½ lbs. in weight. Over Scarpa's triangle, on the left side, a very distinct fullness and vigorous pulsation existed, which involved the whole of the triangle. A small scar, 7½ cm. below the middle of Poupart's ligament, marked the entrance of wound; a similar scar on the back of the thigh on the same level marked the wound of exit. A coarse, continuous thrill, which was accentuated in systole, had its maximal point 2 cm. below the wound of entry, and could be palpated 12 cm. upwards and 14 cm. downwards from the scar, and also on the inner and outer sides of the thigh. A corresponding murmur was easily audible over the whole of the left thigh, and downwards to the middle of the calf on the left side, and upwards over the whole of the lower half of the abdomen; it was just audible over Scarpa's triangle on the right side. The pulsation of the left common femoral was somewhat more forcible than that of the right. Under the skin, in the region of Poupart's ligament, tortuous vessels were to be felt, and on the abdominal side of the ligament a swollen iliac vessel could be palpated. The pulses in the posterior tibial arteries were unequal, that of the right being of good volume and of slightly water-hammer quality, while the left was small and appeared to rise slowly. The radial pulses gave the impression of quickened upstrokes. Capillary pulsation was present in the lips and skin of the face. In the standing position the maximal cardiac impulse, which was heaving in character, lay in the 5th space, 4 cm. beyond the nipple line, or 12 cm. from the mid-line. The 5th and 6th ribs moved slightly with the heart beat. The left margin of dullness lay 12½ cm., and the right 5 cm. from the mid-line. On auscultation, a short inconstant systolic murmur and an accentuated first sound were heard at the apex. At the base a short systolic murmur was heard, the second sound being clear.

The signs remained unchanged when the patient lay down, except that the second sound at the apex became reduplicated. Neither the liver nor the spleen were palpable. The electrocardiograms were normal.

Heart rate.

The heart rate was excessive. While the patient was standing it was 96 per minute: after the patient lay quietly for some time it fell to rates of 65 to 70.

Change on closing the right femoral. A fall of rate was a constant effect when the left femoral was closed. The following figures are representative of the change:—

Date.	Femorals open.	Rt. femoral closed.
March 27th	66	48
April 9th	71	50
July 12th	66	40
	65	45
	68	42
	66	39

The fall was conspicuous, amounting to about 20 heart beats per minute. Compression of the right femoral produced no change of heart rate. Similar effects were observed on several subsequent occasions. Many continuous optical records from the radial artery were taken, the left femoral being compressed or released during the taking of the record. The act of compression or release was signalled, and the response of the heart to change of rate was found to begin usually at the next beat, occasionally at the next beat but one (see Figs. 30 and 31).

Full slowing was usually reached within 2 or 3 seconds of compression. Full acceleration was reached within 5 or 6 seconds of the act of decompression.

Arterial pressure.

On March the 27th and April the 9th the average systolic pressure in the left brachial averaged 116 and 115, while the diastolic pressure averaged 55 and 50 mm. Hg.. The systolic pressure in the left popliteal averaged 73 and 79, while that of the right gave an average of 149 and 144 mm. Hg.. Thus the average systolic pressure of the left popliteal was about 70 mm. Hg. lower than that of the right popliteal, and about 40 lower than that of the left brachial.

Effects of femoral occlusion. The following table illustrates the effect of obliterating the common femoral arteries upon the brachial blood pressures.

Left brachial pressures (alternately with and without obliteration of a femoral artery).

Observer.	Femorals open.		Lf. femoral closed.		Femorals open.		Rt. femoral closed.	
	(syst.)	(diast.)	(syst.)	(diast.)	(syst.)	(diast.)	(syst.)	(diast.)
A. N. D.	120	58	126	74	108	44	108	44
T. L.	114	52	120	72	110	46	108	45
A. N. D.	115	54	118	72				
T. L.	114	58	118	74				
Averages—March 27th	116	55	120	73	109	45	108	45
T. L.	116	52	124*–120	72			112	52
T. L.	115	48	127–116	70			116	52
A. N. D.	114	50	125–118	72			114	52
A. N. D.	115	50	125–118	72			112	48
Averages—April 9th	115	50	125–118	71			113	51

Occlusion of the left femoral artery raised the systolic brachial pressure 3 or 4 mm. Hg. (temporarily 10 mm.); the diastolic pressure rose 18 or 21 mm. Hg., the pulse pressure being thus reduced by from 14 to 18 mm. Hg.. Occlusion of the right femoral artery did not influence the brachial pressures.

The systolic and pulse pressures of this patient were less than in *Case 1*, and the rise of diastolic pressure and diminution of pulse pressure on closing the femoral artery leading to the aneurism were also less conspicuous.

Differential arterial pressures and their changes. The average systolic pressure in the right popliteal on March the 27th and April the 9th was 149 and 144; in the left brachial it was 116 and 110 mm. Hg.. The pressure in the right popliteal was therefore about 33 mm. higher than in the brachial. The following table shows the effect of closing the femoral arteries upon this differential pressure.

Observer.	Right popliteal pressure.		Left brachial pressure.			
	Femorals open.	Lf. femoral closed.	Femorals open.		Lf. femoral closed.	
	(syst.)	(syst.)	(syst.)	(diast.)	(syst.)	(diast.)
T. L.	150	156	120	58	126	74
A. N. D.	152	158	114	52	120	72
T. L.	148	158	115	54	118	72
A. N. D.	148	158	114	58	118	74
Averages—March 27th	149	157	116	55	120	73
A. N. D.	142	138*–138	112	48	125*–118	70
	142	154–148	110	54	125–116	72
	152	162–158	112	54	125–116	70
	140	154–148	108	45	115–110	72
Averages—April 9th	144	152–148	110	50	122–115	71

* Temporary pressure.

As in *Case 1*, closure of the artery leading to the arterio-venous aneurism did not diminish Hill's differential pressure, such change as was observed being in the direction of an increased difference.

Arterial curves.

The pulse of this patient had a slight water-hammer quality, which was but little accentuated when the arm was raised to a vertical position. Optical pulse curves were taken from the right radial artery. The upstroke was a little abrupt in its initial stages, the summit prominent, and the fall to the diastolic steeper than normal. With the arm horizontal, the intervals between the beginning of the upstroke and the summit of the pulse wave averaged 0.121 of a second; the half-way point of the upstroke was reached in the average in 0.042 of a second, a normal value. In the vertical position the last reading was 0.035 of a second, a value below normal. These readings are comparable to those of Feil and Gilder in their third class of aortic regurgitation.

Measurements of optical radial curves (March 27th).

Pulse rates.	Begin. of stroke to $\frac{1}{2}$ way pt. in secs.	Begin. of stroke to summit in secs.	Femoral arteries.	Arm.
74	0.038	0.115	Open.	Horizontal.
47	0.046	0.117	Lf. closed.	Horizontal.
73	0.035	0.105	Open.	Vertical.
52	0.052	0.258	Lf. closed.	Vertical.
63	0.046	0.127	Open.	Horizontal.
43	0.055	0.130	Lf. closed.	Horizontal.
67	0.049	0.128	Open.	Horizontal.
66	0.050	0.126	Rt. closed.	Horizontal.

Effect of closing the left femoral artery. The pulse became slower, and its amplitude was decreased when the femoral artery was closed; the rate at which the initial phases of the pulse were written was slowed. The pulse was much more sustained, and the primary wave being followed by a prominent predicrotic wave which, almost equalling the primary wave in height, produced a form of plateau (Figs. 28 and 29). With the arm vertical, closure of the femoral changed the pulse to an anacrotic form, the new summit of the pulse being then much delayed. The change in form of the pulse beat, on compressing or releasing the left femoral artery, occurred promptly (see Figs. 30 and 31).

Capillary pulsation.

The patient presented a slight spontaneous capillary pulse in the skin of the forehead. Conspicuous pulsation was visible in the lip when this was pressed upon by a sheet of glass, and similarly in the finger nails when suitably pressed upon. Upon obliterating the left femoral, the pulsatile flushing of the skin, lips and nails remained apparently undiminished.

Venous pressures.

On April the 9th the calf of the right leg measured 31 cm., while that of the left measured 30.5 cm.. There seemed to be but little difference in the veins of the two legs: the veins on both sides were sclerosed, and those of the right appeared, perhaps, a little the fuller. The patient was maintained in the horizontal position, and a series of venous readings was taken by Hooker's method from the dorsal veins of the left hand and from both feet, all of which were maintained at precisely the same level, namely, 11 cm. below the sternum.

Venous pressures in cm. water (Hooker's method).

Observer.	Dorsal vein left hand.	Dorsal veins of foot.		
		Right.	Left.	
T. L.	12	11	20	
T. L.	15	12	20	
T. L.	12	12	20	
T. L.	12	12	—	
A. N. D.	12	13	20	
A. N. D.	13	14	22	
A. N. D.	11	11	20	
A. N. D.	12	12	—	
	12.4	12.1	20.3	Average values.
	± 1.4	± 1.1	± 9.3	Corrected averages.

Thus, the pressures in left hand and right foot were equal, while that of the left foot was raised by about 8 cm. of water.

Effect of closing the left femoral artery. Many readings were taken by Hooker's method of the venous pressures in the veins of left hand and right foot, before and after closing the left femoral artery, the state of the artery being unknown to the observer. Such differences as were observed were no greater than the usual variations and were with equal frequency in opposite directions. A needle was introduced a little later on the same day into the basilic vein of the left arm and the pressures were observed directly. Immediately beforehand, fresh readings by Hooker's method were taken from the veins of the left hand, the latter being 11 cm. below the sternum. These readings gave an average value of 14.4 cm. of water (the corrected value being +3.4 cm.). The direct readings were then taken, the basilic vein lying 10.2 cm. below the sternum. During the whole of these observations the pressure was oscillating about 2 or 3 mm. with respiration. The average reading when the femoral arteries were open was 12.3 cm. of water (the corrected value being +2.1 cm.). On compressing the left femoral artery the pressure usually remained unaltered: occasionally a rise of a few millimetres was observed. This rise was a gradual one, being delayed for a few seconds and spread over a few more and being then maintained; no appreciable rise was seen on the three occasions on which the right artery was compressed. As in *Case 1*, no change in the tone of the abdominal muscles could be detected, and the breathing though irregular showed no concomitant changes.

Basilic vein pressures in cm. water (direct method).

Femorals open.	One femoral artery closed		
	for a few secs.	for longer periods.	
12.1	—	11.9	Left artery closed 30 secs.
11.8	—	—	
12.7	—	13.2	
12.3	—	12.6	
12.5	—	12.4	
12.1	—	12.0	" " " 60 "
11.9	12.2	12.1	
12.2	12.3	12.2	
12.2	12.3	12.2	
12.3	12.9	13.0	
12.2	12.3	12.2	Right " " " 30 "
12.6	13.2	12.9	Left " " " 30 "
12.8	12.8	12.7	Right " " " 30 "
12.6	13.1	12.8	Left " " " 120 "
			" " " 30 "
			" " " 30 "

Size of heart, etc.

The chest of this patient was small, and the clinical signs were definitely those of an enlarged heart. The antero-posterior of the diagram gave the following measurements:—the transverse diameter was 13.7 cm., the longitudinal was 13.2 cm.. These values are in excess of the normal for men of the same weight.

Change in size of heart. On closing the left femoral artery, the diastolic position of the right auricular shadow appeared to remain unaltered; the systolic outline moved distinctly inwards by a fraction of a centimetre.

Changes in heart sounds. On closing the left femoral artery no appreciable change in the loudness of the heart sounds could be detected.

Bloodflow to the unaffected leg, etc.

On compressing the left femoral artery we were unable to detect any deepening in the colour of the face. Volume curves taken from the right leg showed no change on cutting out the aneurism; in this respect the patient showed a similar reaction to *Case 1*, though in that case the leg volume fell very slightly.

The blood flow to the right leg (volume approximately 3,000 cc.) was repeatedly tested on July the 12th,* with the left femoral artery closed and open. A water plethysmograph was employed and pressures of 40 and 50 mm. Hg. were thrown on to the veins. The average flow with the anastomosis in play was 5 cc. in 5.2 seconds and, with the artery to the aneurism occluded, it was 5 cc. in 4.1 seconds.† The blood flow through the sound leg of this patient was a good deal larger than that found in *Case 1*, amounting, when the aneurism was closed, to 2.44 cc. per minute to 100 cc. of tissue, a normal value, according to Hewlett. With the aneurism open it amounted to 1.92 cc. per 100 cc. of tissue per minute. The rise in flow on closing the path to the aneurism was thus increased by approximately 30 per cent.. In the first case, in which the arterial disturbances were greater, it was approximately 100 per cent..

In the following three cases, the arterio-venous aneurism was more deeply seated, and occlusion of the artery leading to it was not possible. We include these cases because in many particulars they strengthen our description of the circulatory changes which occur in arterio-venous aneurism.

* We were not entirely content with the inflow curves of this patient, as the steady sweep of the curves was invariably broken by a period of slower rise, after 7 or 10 cc. of blood had entered the limb. This deformity of the curves was maintained after taking off and replacing the plethysmograph and appeared to be a genuine volume effect, but it remained unexplained. Our readings were taken on the stretches of curve preceding this period of slower rise. The figures must be viewed, however, with some reserve.

† At a first sitting the inflow into the leg of this patient could not be obtained, owing to constant though irregular fluctuations of the volume. These variations were continued when the patient slept.

CASE 3.

T. J. H., a stock-keeper of 27 years of age, was first examined on July the 28th, 1921. He joined the army in September, 1914, and was perfectly fit until June, 1916, when he received a shrapnel wound in the back of the neck. Not losing consciousness, he walked to the dressing station and was subsequently in hospital for about six months. At first the neck on the left side was much swollen, and for about three weeks he was absolutely without voice. A few days after being wounded he began to hear a noise in his chest which has since been maintained. After discharge from hospital he improved much, but his voice never completely recovered. He was discharged from the army in January, 1917. When first seen by us he complained of hoarseness of the voice, a continuous buzzing noise in his head, with shortness of breath and precordial pain on effort. There was no history of any past illnesses.

Physical signs (July the 28th, 1921, and March the 5th, 1923). Between these two dates his physical signs remained unchanged. He was a well-built man, 5ft. 8½ in. in height, and weighed 154 lbs. The conjunctivæ were suffused and the skin over the malar eminences injected. The scar of the entering bullet was near the middle of the left subclavian triangle at the edge of the trapezius muscle. No mark of its exit could be found and pieces of metal could be felt under the skin in the episternal notch; under the X-rays one fragment of bullet was seen to lie between the trachea and manubrium and another in the left supraclavicular region. The left vocal cord was seen to be paralysed. A continuous thrill was felt over the whole supraclavicular triangle, having its maximal intensity in the region of the jugular bulbi, extending upwards on both sides of the neck to the angle of the jaw and downwards over the sternum and on both sides of it to the level of the second rib. On auscultation, a continuous murmur (see Fig 26), accentuated at each systole, was heard over the same area, and extending further to include the whole front of the chest, down both arms to a little below the elbows. Posteriorly it was heard over all the chest wall, being most intense in the interscapular regions. While the patient stood, the veins of the left side of the neck seemed more distended than those of the right, and the left cephalic vein was more prominent than the right, though the veins of the hands were equally distended. The heart's impulse lay in the 5th and 6th spaces, just internal to the nipple (10 cm. from the middle line); the dullness to percussion lay a little beyond the impulse; the right margin was found 5 cm. to the right of the middle line. With the patient recumbent the impulse remained unchanged, as did the area of dullness. There was no abnormal area of dullness over the upper chest wall. The first heart sound at the impulse was loud and the second sound reduplicated; at the base only the continuous murmur was audible. While the patient was in this posture a systolic pulsation of the right cephalic vein, centrifugal and extending to the elbow, was visible.

The arteries of the neck pulsated vigorously, moving the lobes of the ears. The pulsations of the two superficial temporal arteries were strong and seemed equal. The radial pulses seemed equal; they presented a conspicuous water-hammer quality, which was accentuated by raising the arms, when a definite thrill became palpable. The digital arteries pulsated appreciably. A spontaneous capillary pulsation in the skin of the forehead and cheeks was seen, and a similar phenomenon was readily elicited by pressing on the finger nails and on the lips.

Heart rate. The average resting heart rate was 72 per minute. The average systolic blood pressures in the two brachial vessels were almost equal to each other, while those in the popliteals were a good deal higher. The diastolic pressures in the arms were low.

Average blood pressures.

Rt. brachial.		Lf. brachial.		Rt. popliteal.		Lf. popliteal.	
(syst.)	(diast.)	(syst.)	(diast.)	(syst.)	(diast.)	(syst.)	(diast.)
140	59	132	58	185	100	177	100

Arterial pulse. Several optical curves were taken from each radial artery; the intervals between the beginning of the upstroke and the half-way point of the upstroke, and between the former and the summit of the pulse were measured. The values for the half-way point were much under normal, especially when the arm was held vertical, and in the curves taken with the arm vertical a series of rapid oscillations was present on the last part of the upstroke and on the summit of the curve (see Fig. 14).

Pulse rate.	Beginning of upstroke to ½-way point in secs.	Beginning of upstroke to summit in secs.	Arm.
75	0.031	0.077	Lf., horizontal.
77	0.014	-	Lf., vertical.
67	0.019	0.074	Rt., horizontal.
67	0.013	0.074	Rt., vertical.
68	0.036*	0.086	Rt., horizontal.
73	0.018	0.077	Rt., vertical.

*This value is exceptional because the half-way point fell immediately beyond a hesitation on the upstroke of the curve.

Venous pressures. The hands were placed level with each other and, the patient being recumbent, 13 cm. below the level of the sternum. The pressures were equal in the veins of the two hands, averaging 13.6 cm. of water by Hooker's method. The basilic vein was then punctured and attached to a citrate manometer. It lay 7 cm. below the sternum and the pressure in it averaged 8.5 cm. of water.

Size of the heart. An orthodiagram of the heart taken with the patient erect gave the following measurements:—mid-line to right margin, 4.5 cm.; mid-line to left margin, 9.0 cm., and longitudinal diameter 15.0 cm..

Sound record. A record of the murmur, taken over the left jugular bulb and a simultaneous optical venous curve, taken from the supraclavicular veins of the right side, is shown in Fig. 26. The murmur is seen to be continuous, though its main oscillations (numbering 125 per second) increase conspicuously in amplitude during systole; the increase in amplitude begins almost immediately after the rise of the c wave. The optical record is a little disturbed by the transmitted vibrations; it records also the 1st and 2nd heart sounds.

Comment. The precise situation of the arterio-venous anastomosis in this case could not be ascertained. The maximal point of the thrill and the situation of the wound indicated a junction between the left jugular and carotid arteries. The equality of venous arm pressures was compatible with this diagnosis, the only point opposed to it being the seeming equality of pressures in the two superficial temporal arteries.

The case is reported because it displayed conspicuous arterial signs, capillary pulse, large pulse pressure, rapid upstroke of the radial pulse, Hill's differential arm-leg pressure, and a heart whose size was on the maximal limits of normality.

CASE 4.

F. G. F., aged 24, first came under observation on May the 17th, 1920. He joined the army in March, 1917, as a perfectly fit lad of 18 years. In his youth he played cricket and football without trouble and took active exercise in other forms. He was wounded in the chest in December, 1917, by shrapnel, the missile entering the chest anteriorly at the level of the 2nd rib, about 2 inches to the left of the mid-line, and leaving it posteriorly below the angle of the left scapula. A fragment of shrapnel remained in the left lung, lying near the hilus and about an inch to the left of the border of the left ventricle near its base. Following upon the wound he was in hospital for six months and was operated upon several times. On leaving hospital he experienced breathlessness on exertion, easy exhaustion accompanied by giddiness and faintness. These symptoms he ascribed exclusively to the wound, and they had improved up to the time when he first came under observation.

May the 17th, 1920. His height was 6ft. 1½ in., his weight 147 lbs. He was of healthy appearance. Over the position of the 2nd left rib in front was a large depressed scar; the middle portion of this rib had been excised. A second large scar was seen just below the angle of the left scapula. Over the 2nd left rib in front a continuous, coarse murmur, accompanied by a thrill, was audible; the murmur was almost equally audible in the 2nd right space, its systolic element being well conducted as far as the left nipple and distantly heard in the left and right axillæ and in the neck. A systolic murmur was well heard at the left interscapular region.

The heart's impulse lay 1 cm. beyond the nipple in the 5th space; the heart was considered to be probably slightly enlarged. The radial pulses were equal and of water-hammer quality.

February the 2nd, 1923. The patient, then a medical student, presented unaltered symptoms; he was breathless on hurrying. At rest his pulse rate was 76 per minute. The cardiac impulse lay in the 5th and 6th spaces, heaving in the former. Its outer limit lay 5 cm. beyond the nipple or 12.5 cm. from the mid-line. The 5th and 6th ribs moved very appreciably forwards at each systole. The left limit of cardiac dullness lay at the impulse, the right limit being 3 cm. to the right of the sternum. Thus the heart showed signs of enlargement between the two examinations. The remaining signs over the chest were unchanged. The right and left radial pulse had a full water-hammer quality, exhibiting a thrill when the wrist was held up. Standing and lying, a conspicuous flush of the whole face with each pulse beat was visible, the same phenomenon being seen in the nails, without pressing upon them and while the arms were horizontal. The veins of the back of the hands were not seen to pulsate, even when held at different levels. The arteries of the neck pulsated vigorously, moving the lobes of the ears, and both superficial temporal pulses were visible. The digital arteries pulsated vigorously and were felt beating to the very tips of the fingers. There was no appreciable fullness of the veins of either arm nor of those on the chest. The pulse in the posterior tibial and dorsalis pedis arteries was strong, but had not the shock-like character of that in the upper arteries. No capillary pulsation was visible in the nails of the toes.

Arterial pressures. The following blood pressures were recorded:—

	Right brachial.		Left brachial.		Right popliteal.
	(syst.)	(diast.)	(syst.)	(diast.)	(syst.)
Averages—February 2nd . . .	133	38*	136	43*	157
.. March 19th . . .	136	37	137	40	154
.. April 10th . . .	136	35	132	39	153

* The sound never vanished; it increased in intensity down to about 55 or 60 mm. Hg..

Arterial pulse curves (February 2nd). Optical curves of the right radial pulse gave the following measurements:—

Pulse rate.	Beginning of upstroke to $\frac{1}{2}$ -way point in secs.	Beginning of upstroke to summit in secs.	Arm.
75	0.031	0.082	Rt., horizontal.
74	0.015.	0.066	Rt., vertical.

The form of the pulse wave altered materially when the arm was raised, the first portion of the upstroke becoming much more rapid, a conspicuous notch appearing on the upstroke near the summit and two smaller ones on the summit, and the dirotic becoming much less distinct (Figs. 15 and 16).

Venous pressures. The average venous pressure in left hand, right hand and left foot, all placed 14 cm. below the level of the sternum, were 10.6, 11.5 and 13.5 cm. water, respectively, on March the 19th; on April the 10th, with the limbs 11.5 cm. below the sternum, the pressures were 14.0, 14.0 and 16 cm. water, respectively.

Size of heart (February 2nd). The orthodiagram showed considerable cardiac enlargement. The right margin lay 6.3 and the left 8.5 cm. from the mid line; the longitudinal diameter was 16.2 cm..

Comment. The precise situation of the arterial leak could not be determined in this case. The equality of brachial pressures suggested a lesion involving the aorta itself. The communication might be between the aorta and superior cava or between the first vessel and the pulmonary artery or its branch. The case is reported because it exhibited conspicuous arterial signs, capillary pulsation, high pulse pressure, a rapid upstroke of the pulse, Hill's differential arm-leg pressure, and a heart notably enlarging.

CASE 5.

A. L., a man 26 years of age, first came under observation on February the 14th, 1921. He joined the army in 1916, and was perfectly fit until August, 1919, when, as he was walking at night, he was shot at very close range in the left shoulder by a kneeling Arab. At first he brought up a little blood, and also complained of a burning sensation along the inner side of the left arm; but the wound healed quickly and after about three months this sensation disappeared and left him with a dull pain at the left shoulder and left side of neck, and a continuous noise in his chest which disturbed him, especially at night. About this time he noticed also that the veins beneath his left clavicle were swollen. He was in hospital for about six months, and was discharged from the army in July, 1920. On exertion the left arm, which remained weaker than the right, became painful and numb; he tired easily, and had slight shortness of breath when hurrying along. There was no history of past illnesses. The patient was examined on February the 14th, 1921, and periodically till February the 26th, 1923. His symptoms remained unchanged except that he thought the noise in his chest became louder.

*February the 26th, 1923.** The patient was a man of 5 ft. 8 in. in height and 154 lbs. in weight. The wound of entry was seen as a small round scar in the first intercostal space 2 cm. below the junction of the inner and middle thirds of the left clavicle; the exit wound lay higher and more to the left, being just above the spine of the left scapula; these marked an oblique track

* The signs elicited upon first examination on February the 14th, 1921, and subsequently, did not differ in any material degree from those detailed below.

which would pass a little deep to the clavicle at about its middle line. The bullet had evidently passed through left subclavian artery and vein, anastomosing them. A long and prominent leash of tortuous vessels spreading over the front of the chest beneath, and parallel to the left clavicle, were joined by the left cephalic vein. A continuous thrill could be felt anteriorly over the left chest, having a maximal point immediately below the mid-point of the left clavicle, palpable as far as the left nipple, and extending through the supraclavicular triangle. A continuous rough murmur, accentuated in systole, was audible over the whole of the chest, back and front, except in the lower parts of the axilla, and over both shoulders and both sides of the neck. In the dorsal position, the main cardiac impulse lay in the 5th space in the nipple line, 10 cm. from the mid-line, and was palpable 12½ cm. from the mid-line. There was no rib movement. Cardiac dulness began 10 cm. from the mid-line, and on the right side 6 cm. from the mid-line. No subclavicular dulness was found. While the patient stood, the main cardiac impulse lay in the 5th and slightly in the 6th spaces, in the nipple line or a little outside it. The percussion dulness lay 11½ cm. from the mid-line on the left and 5 cm. from the mid-line on the right side. The heart sounds at the apex were natural, but at the base of the heart were obscured by the murmur. The arteries of the neck pulsated excessively. The face and neck were flushed, and a full capillary pulse was visible in the lips. The veins of the neck were a little full, and the veins of the left arm more prominent than those in the right, while the skin of the left arm was a little redder. No capillary pulsation could be detected in the finger nails. There was a little analgesia along the left wrist, on the outer side of the thumb, and of the little finger. The pulse in the right radial was full and had a water-hammer quality; the left pulse was small and appeared to be slow in rising.

Arterial pressures. The following arterial pressures were obtained. The systolic pressure in the right arm was normal, the diastolic pressure very low. The systolic pressure in the right popliteal artery was higher than that in the right brachial.

	Left brachial.		Right brachial.		Right popliteal.
	(syst.)	(diast.)	(syst.)	(diast.)	(syst.)
Averages—February 26th ...	65	unobtainable	128	59	141
.. March 20th ...	60	..	122	44	136

Arterial curves (February 26th). Optical curves were taken of the radial pulses and the following measurements obtained:—

Pulse rate.	Beginning to away of up-stroke in secs.	Beginning to summit of up-stroke in secs.	Arm.
87	0.026	0.077	Rt., horizontal.
88	0.028	0.078	Rt., vertical.
84	0.071	0.130	Lf., horizontal.

The measurements show that the pulse in the right arm rose more steeply for the first half of its excursion than does the normal pulse. The rise of the pulse in the left arm was unusually slow. The weakness of this pulse, like the low systolic pressure in this arm, is attributed to the pulse energy being partly dissipated in the left subclavian vein.

Venous pressures. On March the 20th the venous pressures were taken in the left hand, right hand and left foot, all lying at a level 15½ cm. below the sternum. The average values were 13.4, 10.4 and 12.4 cm., respectively.

Size of the heart. The orthodiagraph measurements were as follows:—The right edge of auricle lay 4.0 and the left edge of the heart lay 9.2 cm. from the mid line. The longitudinal diameter was 14.2 cm.

Comment. This case was clearly one of left subclavian anastomosis, lowering the pressure in the left brachial artery and raising it in the veins of the left arm. The general arterial signs of arterial leak were not very conspicuous; capillary pulsation was seen and the pulse possessed a slight but distinct water-hammer quality; there was a small difference between the popliteal and right brachial pressures. The size of the heart was in the high limits of normality.

SUMMARY AND GENERAL REMARKS.

The effects of arterio-venous aneurism on the circulation may be spoken of as local and general.

Local effects consist of a reduction of the blood pressure in the artery beyond the point of the arterio-venous anastomosis, a reduction which is associated with a slow rising pulse : and of an increase in the venous pressure in the veins tributary to the affected one. These effects are well known to occur and are readily explained : the last named is commonly accompanied by prominence and often tortuosity of the corresponding veins and with the opening up of venous anastomoses, by suffusion of the corresponding skin area, and by an increase in the girth or actual œdema of the corresponding limb.

The more interesting effects are general effects, and these are summed up and briefly discussed in the following paragraphs :—

General arterial pressure. Taking the pressures in one or both brachial arteries as the guide to general arterial pressure, the systolic pressures are normal in patients at complete rest ; the diastolic pressures, on the contrary, are much below normal. The effect of the aneurismal communication upon the arterial pressures is well illustrated by those cases in which the pressures are taken before and after closing the artery supplying the communication (*Cases 1 and 2*) : the systolic pressure rises a little, the diastolic pressure rises considerably and reaches a normal point, on closing the anastomosis. Readings taken under atropine are the most comparable, since change of rate is thereby excluded. The systolic pressures in our cases may be somewhat below those usually found in free aortic regurgitation, and this difference may be due to the irremediable loss of blood to the systemic arterial system when this leaks into a vein : whereas in reflux into the ventricle, some or all of the loss may be repaired at the next systole : the diastolic pressures, however, are precisely those found in cases of free aortic regurgitation, and the pulse pressure is consequently much greater than normal, an observation which will acquire significance when the amount of leak in the two conditions comes to be considered.

Water-hammer pulse. That the water-hammer pulse is a usual sign in arterio-venous aneurism has long been known to us. Measurements of optical records from these cases show, as was expected, that this quality is associated with rapidity of the upstroke in its initial phases. Numerous observations of this kind were undertaken by Feil and Gilder⁶ in this laboratory a few years ago upon cases of aortic regurgitation. Averages of Feil and Gilder's values for free aortic regurgitation and for normal subjects are incorporated in the accompanying table and compared with those now found by us in arterio-venous aneurism. In all respects the abnormalities of the upstroke of the aortic case are repeated. The upstroke, despite its greater amplitude, is completed a little more quickly than normal ; the

half-way point is reached much more quickly than normal, and this abruptness of the initial phase is usually exaggerated by holding the arm vertically. The brief thrills which commonly complicate the upstroke or summit of the pulse in aortic regurgitation are also recorded in arterio-venous aneurism. Associated with the rapid and large upstroke are the same subsidiary phenomena as are witnessed in aortic reflux, namely, exaggerated visibility of the arterial pulsation in neck and arms, palpability of the digital pulse, audibility of the pulse in the palm of the hand, and the so-called pistol shot sound over the large arteries.

Pulse form.

Case.	Pulse rate.		Beginning of upstroke to half-way point		Beginning of upstroke to summit		Arm.
1	98	86	0.041	0.045	0.065	0.068	Horizontal. Vertical.
2	68	73	0.042	0.035	0.121	0.105	Horizontal. Vertical.
3	70	72	0.028	0.015	0.079	0.075	Horizontal. Vertical.
4	75	74	0.031	0.015	0.082	0.066	Horizontal. Vertical.
5	87	88	0.026	0.028	0.077	0.078	Horizontal. Vertical.
Averages	80	79	0.029	0.022	0.085	0.078	Horizontal. Vertical.
Averages of Feil and Gilder's aortic curves. (Class i and ii)			0.027	0.017	0.078	0.080	Horizontal. Vertical.
Averages of Feil and Gilder's normal curves			0.039	0.045	0.103	0.117	Horizontal. Vertical.

That these abnormalities of the pulse and their associated phenomena are dependent upon the leak in the arterio-venous aneurism cases is shown by their disappearing when the artery leading to the sac is closed, whether there is an accompanying change of heart rate (*Cases 1 and 2*) or not (*Case 1* under atropine). Like the large pulse pressure, the water-hammer pulse is shown by these observations to be directly dependent upon the leak from the arterial system.* The water-hammer pulse is in fact brought

* We are not entirely convinced that in arterio-venous aneurism the leak is wholly responsible for these changes, though it is so unquestionably in greatest part. The pulse remained a little anorpt in its upstroke in *Case 1* after the closure of the femoral artery concerned; the lowest normal value for the half-way point given by Feil and Gilder is 0.031 of a second with the arm horizontal and 0.039 of a second with the arm vertical; their average values were 0.039 and 0.045 of a second, respectively. The values reached on closing the leak in our patient were somewhat lower than these figures. It still seems possible, though perhaps improbable, that the water-hammer pulse is in small part due to change in the nature of the heart beat or to change in the condition of the arterial wall or peripheral vessels, consecutive to the establishment of the leak.

about by the fall of diastolic pressure, and this in turn by the rapid escape of pulse energy from the arteries to the veins. The water-hammer quality is an impression conveyed to the finger by rapidity of upstroke in its initial phases. The rise of pressure becomes slower in the last phases of the upstroke, the actual summit being reached at an almost normal interval. The rapid ascent occurs over that phase of the heart's systole during which the aortic pressure is abnormally low: the ventricle has at this phase to meet little resistance, the blood passes out with abnormal rapidity and the aortic pressure rises with abnormal speed. To this same unresisted and sudden movement we ascribe the reduction of the presphygmie interval observed in *Case 1*.

These observations on the increased pulse pressure and the rapidity of upstroke in cases of arterio-venous aneurism, and their prompt disappearance in large part or in whole, immediately the aneurism is cut out from the circulation, appear to us finally to dispose of the view that the phenomena in question are materially dependent upon any consecutive or compensatory changes in the peripheral vessels, such as has been held responsible in the case of aortic regurgitation. It is scarcely to be doubted that we are dealing with manifestations having precisely the same underlying cause in the two conditions: a conclusion which applies to the one will equally apply to the other.

Collapsing quality. The summit of the pulse in arterio-venous aneurism is ill-sustained, the curve falling quickly to the dicrotic notch. This fall is the steepest in the curve. Since the leak occurs mainly in the systolic phase, this quick initial fall of the pulse curve is not surprising. Yet it cannot be ascribed to this cause without further comment. In Feil and Gilder's optical curves⁶ from cases of aortic regurgitation, the steepness of the systolic fall was also noticed: and thus a resemblance is again found between the arterial phenomena of the two conditions. That there should be this resemblance is somewhat remarkable since in aortic regurgitation the leak is confined to diastole. If the term collapsing quality is used to intimate that the pulse falls away quickly from the palpating finger, then it is probable that in both conditions the steep initial fall is responsible for the sensation.* If the pulse is called collapsing because its steepness, as compared to the normal, is more exaggerated at one particular phase of the pulse beat than at another, then it is true, as Wiggers²⁰ has shown, that the quality "collapse" is inherent in that part of the pulse beat which follows the dicrotic notch: for, compared to the normal, this phase of the pulse shows more change when aortic regurgitation is made than does the systolic fall. But that is not equivalent to the statement that when aortic regurgitation is made, the diastolic fall is then the steepest descent in the corres-

*We may here point out that the term "collapsing pulse" is frequently used, but erroneously, as a synonym for "water-hammer" pulse. A water-hammer pulse is one which ascends quickly, a collapsing pulse is one which descends quickly: rapid descent is clinically much more difficult to recognise than rapid ascent.

ponding pulse; Wiggers' curves show this not to be the case. Our point is that, just as the normal pulse shows its steepest decline before the dirotic notch, so do both the pulses of aortic disease and of arterio-venous aneurism; that in both these states this initial fall is more abrupt than normal, and that in both it is probably responsible for the sensation of collapse conveyed to a palpating finger. This statement is not inconsistent with Wiggers' observation, that aortic regurgitation chiefly increases the steepness of the diastolic line. A common factor for the initial rapid fall of pressure may be found possibly in the character of the heart beat, when, as in both conditions, the ventricle has to meet initially low aortic pressures, or it may be found in the swing of the arterial walls. It is not due in arterio-venous aneurism in any degree to rapid output from the peripheral vessels consequent upon their dilatation, such as Stewart¹⁸ assumes for aortic regurgitation; if that were the case, it would be maintained for some seconds and in some degree when the leak is closed. This it does not do; the change to the normal sustained form occurs at once. Thus, so far as arterio-venous aneurism is concerned, it is shown that the abnormal channel of flow, and not a widened peripheral channel, is responsible for the collapsing quality, as this is recognised clinically. In arterio-venous aneurism the rapidity of the initial fall may be ascribed in part directly to the loss of blood and pulse energy through the hole in the vein; but since a similar steep fall is seen in aortic regurgitation, it is probably also due in part to a further factor common to the two conditions. This common factor appears to be independent of consecutive change in the peripheral vessels. Stewart appears to have been influenced largely in his opposite conclusion by the conviction that the amount of blood regurgitating in aortic disease is trivial, a view with which, for reasons to be stated later, we disagree.

Hill and Rowland's differential pressure sign. In all our cases, and in greater or lesser degree, the same discrepancy between systolic arm and leg pressures has been noted as was discovered by Hill and Rowland⁸ in aortic regurgitation. Hill believes that this difference is due to local arterial conditions, as he finds it may be abolished by warming the leg, and concludes that the high pressure results from increased tone in the leg artery. This view implies that the difference in pressure is independent of the form and amplitude of the pulse wave as it enters the arteries. Our observations in Cases 1 and 2 show conclusively that this is so, for on stopping the leak, Hill's differential pressure sign was not abolished; on the contrary it was often exaggerated;* the water-hammer pulse and exaggerated pulse

* Some isolated readings taken of the blood pressure by Pachon's method in arm and leg by Num and his collaborators,¹⁵ before and after compression of the affected femoral artery in two cases of arterio-venous aneurism, seem to be in general agreement with our own, though the rise of systolic pressure appears to have been greater in their cases. These observations, however, are difficult to use in definite support of our conclusion, since the artery from which particular pressures were taken by them is not always clearly stated. The readings of their first case seem also to indicate that a differential arm-leg pressure may persist for at least a day after the arterio-venous aneurism has been extirpated, though here again the above-mentioned difficulty is again experienced.

pressure, on the other hand, were abolished. In *Case 1* also there were occasions when Hill's sign was less distinct or even absent, despite the continued presence of the water-hammer pulse and the high pulse pressures. It is perfectly clear, therefore, that Hill's sign is independent both of high-pulse pressure and water-hammer character of the pulse in cases of arterio-venous aneurism. That being the case, and the resemblance between the arterial changes in arterio-venous aneurism and in aortic regurgitation being so close, we are justified in drawing the same conclusion for the last class of patient also. Thus, we are brought to conclusion similar to that arrived at by Hill, namely, that his differential pressure is due to a consecutive or compensatory change in the circulation. The average readings of the arterial pressures in the brachial and popliteal arteries of the five cases are tabulated below.

Average arterial pressures.

Case.	Artery affected.	Right brachial.		Left brachial.		Right popliteal.	Left popliteal.
		(syst.)	(diast.)	(syst.)	(diast.)	(syst.)	(syst.)
1	Right femoral	149	55	147	53	129*	163
2	Left femoral	—	—	114	52	146	76*
3	Possibly L. carotid	140	59	132	58	185	177
4	Probably aorta	135	37	135	41	155	—
5	Left subclavian	125	51	62*	—	138	—

* Pressure low, distal to aneurism.

Capillary pulsation. This phenomena is noted in many conditions, and, as Quincke first pointed out, is also to be seen in normal people: but we deal for the moment with that very vivid form of capillary pulse which is rarely witnessed apart from aortic disease and such conditions of arterio-venous anastomosis as we are at present discussing. We do not purpose in the present article to discuss this phenomenon as length, since it is under further investigation: but our observations upon *Cases 1* and *2* seem clearly to establish the conclusion that capillary pulsation in its full degree, pulsation which may be spontaneous in the skin of the face, does not necessarily depend upon an exaggerated pulse pressure nor upon a particularly steep rise of the pulse's upstroke, nor upon a collapsing quality of the pulse; for in two cases in which this phenomenon was associated with large pulse pressure and quick upstroke, etc., the complete, or almost complete, abolition of the last factors did not abolish and did not diminish the visible capillary flush. The vividness of the change from red to white is, of course, an imperfect gauge of the degree in which the capillary pressure changes with each heart beat, and, that being the case, we cannot assert that this pressure

change remains unaltered when the leak is closed. It seems very probable that in the last circumstance the pressure change will be less, since the pulse pressure diminishes: for the capillary pulse is but a reflection of the arterial pulse. But although, in this sense, an exaggerated arterial pulse pressure and quick upstroke might be regarded as favouring a rhythmic change of capillary pressure, and in some cases, perhaps, as determining visible pulsation in the skin, yet it is clear that it is a non essential factor. This at present unknown factor associates itself chiefly with the characteristic changes in the arterial pulsation, which are illustrated by cases of arterio-venous aneurism, aortic reflux and also persistent ductus arteriosus; but it is obviously consecutive to these changes in the arterial pulse, persisting after they have been abolished.* Thus, the physical sign capillary pulsation falls into the same group as does Hill's sign of differential arterial pressures. This conclusion appears to us to be applicable to the sign as it appears in all three of the above named conditions.

General venous pressures. The general venous pressure appears to have been normal in all our cases within measurable limits, an observation which harmonises with the normal size of the liver and systemic veins in these patients.† The following table sums up our observations upon the five cases of arterio-venous aneurism and includes control observations on the venous pressure in the hand of six healthy adult males. The pressures given for patients in this table are from veins not directly affected by the aneurism. The most conclusive observations, to show that the leak from artery to vein has no appreciable effect on general venous pressure, are those in which the arterio-venous anastomosis could be cut off at will (*Cases 1 and 2*) and in which this procedure failed to alter the venous pressure in measurable degree.

Incidentally we may say that in a number of experiments upon dogs we have produced free communication between the main arteries and veins of the lower limbs under varying conditions, and often have been unable

to alter the venous pressure. When the communication between the artery and vein is prevented, the mean arterial pressure rises and the blood which would have passed out through the abnormal communication is now forced out through the capillaries.

* After making free arterio-venous anastomoses artificially in the dog, we fail to find visible capillary pulsation in the lips and tongue. The same sign might be sought in experimental aortic regurgitation.

† And these, as numerous direct tests of venous pressure in patients, showing early congestion of the venous system, tell us, are sensitive indications.

General venous pressure (by Hooker's method).

Controls.	Age.	Vein of	Sternum to vein in cm.	Pressure in cm. H ₂ O (actual).	Pressure in cm. H ₂ O (corrected).*
1	32	Left hand.	11.5	11.0	— 0.5
2	27	" "	11.0	10.5	— 0.5
3	32	" "	13.5	13.0	— 0.5
4	41	" "	11.0	11.0	0.0
5	18	" "	11.25	12.0	+ 1.75
6	30	" "	12.5	11.5	— 1.0
Case.					
1	34	Left hand.	14.7	14.1	— 0.6†
2	26	Left hand.	11.0	12.4	+ 1.4†
		Right foot.	11.0	12.1	+ 1.1
3	27	Both hands.	13.0	13.6	+ 0.6†
4	24	Both hands.	12.7	12.5	— 0.2
		Left leg.	12.7	14.7	+ 2.0
5	26	Left leg.	15.5	12.4	— 3.1

* Corrected to level of sternum. Moritz and v. Tabora,¹¹ using the direct method, and correcting their pressures to a level 5 cm. below the sternum, obtained an average pressure of 5.2 cm. H₂O, in a large series of cases.

† The readings from an arm in each of these three cases was checked by Moritz's method; the last readings were within about 1 cm. of those taken by Hooker's method (above or below the last) in each instance.

The criticism has been expressed to us that these pressures may not represent the events in the larger veins, since they have been taken from a vein lying at a distance from the heart; they could be taken from no other. We do not believe that such readings, taken with due precautions, introduce any material error; *a priori*, it is impossible that any sustained rise of right auricular pressure can occur without a corresponding increase of the whole pressure gradient to the periphery; a rise of central pressure would necessarily at once tend to lessen or stop the flow from the periphery, the blood would accumulate there and pressure would be raised until the original flow re-established itself. A sustained central rise may be delayed at the periphery, but it could not be avoided, providing that the veins from centre to periphery remained open; and this is guaranteed by the position in which the arm is placed when the readings are taken. We have found that those who have raised this criticism have been unaware that a water manometer attached to the human basilic vein clearly shows such transient rises and falls of venous pressure as are produced centrally by natural beating; and that even slight pressure upon the abdomen is responded to, after a little delay, by an appreciable pressure rise in the meniscus of the manometer. The criticism is based on the belief, which we at first held ourselves, that an appreciable leak from artery direct to vein must necessarily raise central venous pressure. Observations upon animals, which are to be recorded later, have shown conclusively that this is not the case.

It is to be understood, however, that our conclusion that general venous pressure is not raised, is confined to the cases which we have studied and to

cases of a like order: we are not prepared to say that in arterio-venous aneurisms the leak from vein to artery *never* raises venous pressure, but rather to insist that it is not of necessity increased.

Heart rate. In Makin's collected cases¹¹ of arterio-venous aneurism the pulse rate is usually given at 90 to 100, but as most of these cases are described soon after the wounding, these rates can hardly be regarded as representative. In our own chronic cases the pulse rates with the patient at rest have averaged 84, 67, 72, 76 and 86 in the five cases. These rates are somewhat higher than those usually found in young subjects at rest, but not remarkably so. Closure of the artery leading to the arterio-venous anastomosis which could be performed in two cases, lead to prompt and conspicuous falls of rate, average rates of 53 and 47 beats per minute being attained. These rates are below those usually prevailing. We find also that the production of arterio-venous aneurism in dogs, in which vagal tone is intact, raises the heart rate and that subsequent closure of the leak retards the heart rate. Since these observations were made we find that the similar effects have been observed clinically by Dobrowolskaia⁵, and by Nanu¹⁵ and his collaborators.* While it seems it may be concluded that the leak from artery to vein tends to produce an enhanced rate, it is also probable that a compensatory mechanism eventually comes into play in patients, whereby this increased rate is checked. In support of this conclusion are the rates observed by Cazamian³; in his case the rate before extirpation of an arterio-venous aneurism was 102; for three days after operation the rate was about 60, rising on the fourth day to about 80 beats per minute, a rate subsequently maintained.

Dealing with the phenomenon observed, namely, conspicuous fall of rate on closing the anastomosis, this fall of rate is vagal in origin, for it is abolished by atropinisation. We are justified in concluding that it is wholly vagal, for at the height of the atropine reaction, in the case tested (*Case 1*), the pulse rate was altered by but 2 beats per minute on closing the anastomosis; this slight difference is sufficiently to be explained by incomplete paralysis of the vagus by the drug. Nanu has recently made a similar observation. The rise of rate in opening the anastomosis is to be ascribed to a fall of vagal tone. Bainbridge¹ has apparently shown that an increased filling of the veins accelerates the heart action, and he found that this response is mainly a vagal reflex. But compression of the artery leading to the aneurism was ascertained in two of our patients to produce no fall of venous pressure, and decompression was ascertained to produce no rise of venous pressure. The changes of heart rate on compressing and decompressing the artery cannot be ascribed therefore to altered venous filling but must be

* The first accounts of retardation of the heart beat on closing the artery leading to an arterio-venous aneurism appears to be that of Brandham (*Internal, J. Surg.*, N.Y. 1890, *vi*, 250); an earlier account speaks of syncope occurring in similar circumstances (Hugnier, *Bull. Soc. de chir. de Par.* 1852, *ii*, 106).

attributed purely to altered arterial pressure. With the last they are very closely associated. When the leak is closed, the lowest pulse rate is reached within a few heart cycles of the act of compression. It is at this phase that the systolic arterial pressures rise to their highest. The lowest heart rate reached is not long maintained, neither is the highest arterial pressure: both are fleeting. The pressure which changes most is the diastolic: this rises on closing the leak: but as this systolic pressure also rises a little or remains unchanged, the arterial pressure change may be viewed as a rise of mean pressure. That a rise of mean arterial pressure retards the heart beat was first shown by Marey¹²: the effect is generally acknowledged and is ascribed to the vagus. The extent to which the reaction is a direct effect on the vagal centre or a reflex has been much discussed (see Tigerstedt's summary)¹⁹.

To sum up, in arterio-venous aneurism the pulse rate is higher than normal, and this rapid heart action is due to changed vagal tone, controlled through the medium of mean arterial pressure. These observations provide us with a simple explanation of the increased heart rate, which is generally recognised to occur in aortic regurgitation: for the same factor, low mean arterial pressure comes into play in these cases also. When an arterio-venous aneurism has become established, the initial rapidity of the heart's action appears to be in a measure checked, for the rates obtained on closing the leak are lower than normal: probably the same is true in aortic disease.

Output of heart, blood flow to tissues and the amount of the leak. Attempts were made to measure the output of the heart in *Case 1*, but these, for reasons we do not propose to discuss, were unsuccessful. Reasons have already been given for the conclusion that the heart's output in this case remained unchanged on closing the artery leading to the aneurism: for this procedure left the venous pressure substantially unchanged, and the input to the heart controls the output. Further evidence for the same conclusion has been given in the section which deals with the blood-flow to the limbs in the report of *Case 1*. In experiments on dogs, subsequently to be reported, it has been found that anastomoses of arteries with veins do not necessarily increase the cardiac output: that is always so, if the anastomosis leads to no rise of venous pressure.

Once this conclusion, that cardiac output remains unchanged, is accepted, a further conclusion follows from our observations. It has been seen that the blood-flow to the tissue of the unaffected limbs may be conspicuously altered when the way through the aneurism is open and closed: in our first case the flow to the limbs was approximately doubled when the right femoral artery was closed. It follows that, if our premises are true, the arterio-venous aneurism in this case carried half the arterial stream of the body. If the output of a dog's heart is measured cardiometrically and this output is compared with the output of blood from the cut external iliac artery, the last is found to be a substantial fraction of the first, which in the special

circumstances of low arterial pressures may amount to more than half the output of the left ventricle.* That is so, because, owing to the negligible peripheral resistance, the velocity of flow in the cut artery is greatly increased. Very similar conditions must rule in any cases of arterio-venous aneurism, in which a considerable communication usually exists between artery and vein. It is certain that our first case belongs to this category, and we have arrived at the conclusion that approximately half the arterial blood leaked directly into the vein involved. It is inevitable, in many cases of this type, that a very large fraction of the left ventricular output should be lost in this fashion. To what physical changes do such leaks directly give rise in the general arterial system? They give rise to precisely those changes which are well known to occur in free regurgitation through the aortic valves, namely, to well developed water-hammer pulse and to a pulse pressure which may be exaggerated, as in our first patient, to 100 mm. Hg.. These observations seem to us finally to lay at rest the controversy as to the amount of blood regurgitating in clinical aortic disease. Given that in a case of aortic regurgitation the arterial phenomena are as fully developed as they are in cases of free arterio-venous anastomosis, and frequently this is the case, we cannot avoid concluding that the amount of blood regurgitating is a very considerable fraction of the output per beat. It is true that in our second case the increased flow of blood to the limbs on closing the anastomosis was much less; but this case did not present the full arterial signs seen in free aortic regurgitation. While, from our data, we cannot express the amount of the leak in actual figures, the expression in terms of a fraction of the cardiac output is, perhaps, of equal value. We do not think we are rash in concluding that in arterio-venous aneurism cases and cases of aortic reflux, treated as a whole, and presenting fully developed arterial signs, the amount of blood lost at each systole may approach closely to if it does not equal 50 per cent. of the left ventricle's discharge. We are unable to accept the evidence which Stewart¹⁸ puts forward for his conclusion that the amount of reflux in aortic disease is trivial. He attempts to measure the amount of blood regurgitating by measuring the diastolic filling of the heart cardiometrically, with the aortic valves intact or torn. The curves which he publishes do not seem fully to substantiate his premise that the diastolic filling remains almost unchanged; but even if we accept this statement, his conclusion remains unjustified. It relies upon the assumption that when the aortic valves are broken, the backward transference of blood from aorta to left ventricle is the sole added factor influencing the diastolic volumes of the heart; but this is not the case. While blood regurgitating from the aorta tends to produce larger diastolic volumes, it raises the intraventricular tension in diastole, as Wiggers has shown,²⁰ and this rise of tension must impede the filling of the ventricle through the mitral orifice†. Another

* Recent and personal observations.

† Stewart states that there was no diminution in the amount of blood delivered by the auricle in his experiment, but the only evidence adduced for this statement is that there was no increase in the size of the auricle, the size of the auricle being judged presumably by inspection only.

effect, acting in the same direction, and very probably one of much importance to the measurement, is change in the size of the coronary vessels. When the aortic valves are broken, mean arterial pressure falls and the capacious coronary arteries shrink in size. Thus an increase in diastolic volume produced by regurgitating blood will be counteracted in part or in whole, by opposing factors coming into play at the same time. We do not believe that the amount of blood regurgitating can be estimated with sufficient accuracy by means of volume curves of the ventricles.

Wiggers²¹, in his recent publication (page 554) states, "that all experimental evidence contradicts the view so prevalently held by clinicians that a large proportion of the systolic discharge flows back in each diastole." This conclusion is also based essentially on volume curves of the ventricle, which, so we believe, provide the only experimental evidence in apparent conflict with the clinical conclusion criticised. That the conflict is more apparent than real seems probable to us for reasons already stated; the difficulty lies in part at least in the interpretation of the volume curve. It is often overlooked in these discussions that in aortic disease in man not only the valves are the seat of disease but the aorta is itself unhealthy and its rings conspicuously dilated; the weakness of the valve lies not only in its cusps, but in the diseased wall which supports them. After fully considering the opposite view, we have no hesitation in adhering to the conclusion that in many cases of aortic regurgitation the amount of backward leak is very substantial.

Enlargement of the heart. In 1917, Makins, in his description of a unique collection of cases of arterial and arterio-venous aneurism consequent on wounds, drew special attention to the size of the heart. In his tables the apex beat is stated to be in the 5th rib space in the nipple line, slightly or decidedly beyond it, in all but three out of seventeen cases of the last group. Regarded individually many of these cases fail to show convincing evidence of cardiac enlargement, regarded collectively Makins has produced sufficient evidence to establish his conclusion. In a case previously reported by Osler¹⁶, enlargement of the heart and progressive cardiac failure followed an arterio-venous anastomosis after 13 years. His case could not be regarded as by itself conclusive, seeing that the cardiac complications may have been due to other causes. Our own evidence accords with that of Makin's, for, in all our cases, the orthodiagraphic measurements show the diameters of the heart to have been on the upper limits of normality or beyond these.

Orthodiagraph measurements in cm. (erect posture).

Case.	Weight in lbs.	Mid-line to rt. margin.	Mid-line to lf. margin.	Transv. diam.	Long. diam.	Normal values (Claxton and Merrill).		
						Mid-line to rt. margin.	Transv. diam.	Long. diam.
1	112	4.5	9.0	13.5	14.0	3.2-4.3	10.7-11.3	11.8-13.5
2	114	3.5	10.2	13.7	13.2	3.2-4.3	10.7-11.3	11.8-13.5
3	154	4.5	9.0	13.5	15.0	3.2-4.5	11.5-13.0	12.5-15.0
4	147	6.3	8.5	14.8	16.2	3.4-4.6	11.0-13.1	12.0-14.5
5	154	4.0	9.2	13.2	14.2	3.2-4.5	11.5-13.0	12.5-15.0

Any doubt which might exist as to the relation between arterio-venous aneurism and enlargement of the heart has been set at rest completely by the observations of French surgeons. Cazamian³ noticed that an enlarged heart diminished in size in a case of arterio-venous aneurism when the anastomosis was closed by operation. A still more striking case has been reported by Leriche¹⁰. He extirpated an arterio-venous aneurism in a patient in whom there was considerable cardiac enlargement and general signs of cardiac failure, and his operation was followed by a return of the heart to normal size and by disappearance of the signs of failure. Observations by Grégoire and Lian (cited by Nanu) and by Nanu and his co-workers¹⁵ are fully confirmatory of the remarkable changes in the heart's size which follow removal of the aneurism. Lastly, Reid¹⁷ has noticed enlargement of the heart to follow experimentally produced anastomoses.

The cause of the enlargement is not obvious. At first we were inclined to attribute it on theoretical grounds to raised general venous pressure; but our direct observations have shown that such a rise of general venous pressure did not exist in our patients, in all of whom enlargement was present. That general venous pressure may be raised when the circulation shows failure, as it may do as a sequel to arterio-venous aneurism, is allowed; such failure and rise of venous pressure, however, may be secondary to cardiac enlargement and not responsible for it. It is, however, probable that a very large arterio-venous anastomosis, and especially one which lay on the main vessels of the trunk, might raise general venous pressure directly. That, however, is beside the present point. We present a series of cases in which there is enlargement of the heart and in which venous pressures are normal. It is clear, therefore, that venous pressure is not responsible for enlargement in these cases and that some other factor must be in play. This second factor may be presumed also to come into play even in cases where general venous pressure is raised. Now it is shown by our X-ray observations that the enlargement of the heart is not an immediate effect of a short-circuited flow. Such change in the size of the heart as occurs when the aneurismal communication is opened and closed is small, and is, we think, attributable to altered heart rate, the systole being more complete when the heart rate becomes slower. The enlargement in these cases is a consecutive affair. If the patients are at rest, the mean arterial pressure is below normal*: the output of the heart, so far as we can ascertain, is not above normal. In so far, therefore, as the work of the heart, in transferring blood from venous to arterial system, is concerned, it may be said that the evidence speaks for a reduction in the amount of this work. Enlargement of the heart cannot therefore be assigned to this cause in cases of the type we are describing.

It is due, in our view, to a factor which so far has received no attention; namely, to diminished blood flow through the nutrient vessels of the heart.

* We base this statement not only on our own cases, but on those of other observers (Makins, etc.); the only exception to the rule of which we are aware is Nanu's first case.

If we take the supply to the limbs as our index, then the flow through the coronary vessels may be diminished by an arterio venous aneurism to even one half its normal amount: moreover, Markewalder and Starling¹³ have brought evidence to show that the flow in the coronary vessels is peculiarly dependent upon aortic pressures; that being the case, the fall of mean arterial pressure is of even greater consequence to the metabolism of the heart than it is to the metabolism of the body generally. A dilatation of the heart consecutive to the formation of a free arterio-venous anastomosis appears to us a natural consequence, when its effects are viewed from this standpoint. That dilatation is the main element in the enlargement is clearly evidenced by the rapidity with which the size decreases when its cause is removed: thus Nann and his collaborators noticed the change to occur within a few weeks of operation in their two cases. Leriche speaks of a diminution in the size of his patient's liver during the operation, though he attributes this change to a reduction in the general venous pressure.* To what extent enlargement of the heart may be due also to increase in the mass of the muscle, has not as yet been determined: if it occurs it may be consecutive to dilatation.

That there are causes of cardiac enlargement other than increase in the amount of the work it performs is well known, but they have been in the past ill-defined. Cardiac enlargement, conspicuous as it may be, in cases of arterio-venous aneurism in which it can be shown that the work of the heart is not increased, seems to us to bring the factor of muscle nutrition into the foreground of the discussion. Thus, deficient blood supply to the organ is a sufficient explanation of cardiac enlargement in the severe anæmias; it very possibly plays a prominent part in the enlargement of free aortic regurgitation; it would come especially under suspicion where, for any reason, the output of the heart is seriously diminished, or where enlargement of the heart is associated with constrictive lesions of the coronary vessels; it should also be suspected as a contributing or determining cause in instances of diminished arterial pressure associated with dilatation, as, for example, in severe acute fevers.

CHIEF CONCLUSIONS.

1. Arterio-venous anastomoses when free are associated with the characteristic signs of aortic reflux in the systemic arterial system, namely, low diastolic pressure, large pulse pressure, water-hammer pulse, collapsing pulse, capillary pulsation, and a difference in the arm-leg systolic pressures, etc.
2. The first four of these signs are shown to be dependent upon the leak of blood from the arterial system, and the last two to be due to consecutive changes in the circulation. This conclusion, while certainly true for arterio-venous anastomoses, seems to us equally applicable to aortic regurgitation.

* In this Leriche is very probably correct, in part. His case was one in which signs of failure had developed.

3. A conspicuous fall of diastolic pressure, such as occurs in arterio-venous aneurism, causes a shortening of the presphygmic interval and a slower conduction of the pulse wave.

4. The heart rate in arterio-venous aneurismal cases is raised. This rise, though in part compensated, is due to loss of vagal tone, consequent upon the fall of mean arterial pressure. A similar conclusion probably applies to the accelerated heart rate in many cases of aortic regurgitation.

5. The escape of blood from arteries to veins in arterio-venous aneurism cases, even when free, does not necessarily, or even customarily, raise general venous pressure. That is so because overfilling is compensated by a less rapid escape of blood from the capillaries of the body generally, the mean arterial pressure being much reduced.

6. The quantity of blood leaking from a large limb artery to the corresponding vein in arterio-venous aneurism cases may be very considerable, amounting to a fifth or even a half the quantity thrown out by the left ventricle at each beat. The amounts of blood leaking back into the left ventricle in cases of free aortic regurgitation are comparable to those leaking into the veins in these arterio-venous aneurism cases.

7. The output of the heart in arterio-venous anastomoses does not appear to be usually altered, but the amount of blood flowing through the whole capillary bed may be seriously diminished, even to one half its normal quantity.

8. An escape of arterial blood directly into the veins decreases, and sometimes materially, the CO_2 content of the alveolar air and of the arterial blood; but, owing to the lessened supply of blood to the respiratory centre, does not necessarily alter in material degree the rate or depth of respiration.

9. The heart enlarges in cases of free arterio-venous anastomosis. This enlargement, presumably primarily and chiefly a dilatation, is due, so it is suggested, to a deficient nutrition of the heart muscle, consequent on the fall of mean arterial pressure. A deficient supply of oxygenated blood to the coronary vessels is probably the cause, or a contributing cause, of cardiac enlargement in a variety of conditions, for example, in the anæmias, aortic regurgitation, constrictive lesions of the coronary vessels, and any condition in which the output of the heart is decreased or mean arterial pressure is much reduced.

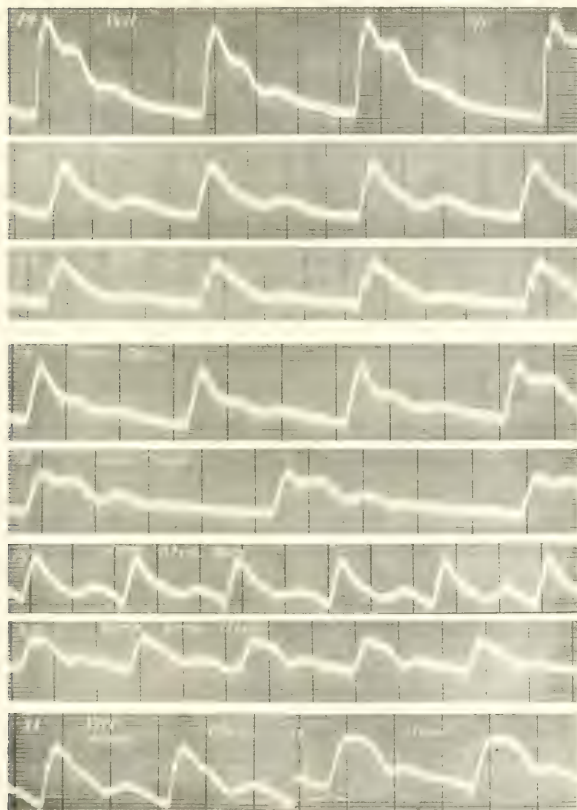
We have finally to express our thanks to Dr. C. H. Kellaway for the aid he has given us in determining certain respiratory changes in our first case; his notes are included in our article with his permission.

NOTE.—While this paper has been in the press, our attention has been called to Holman's report of an arterio-venous aneurism of the popliteal vessels (*Archives of Surgery*, 1923, vii, 64-82). The pulse rate and blood pressure readings in his case were similar to those of our own Case 1, and these presented similar changes on closing the anastomosis. The patient was operated upon and, within 13 days, showed a diminution in the size of the heart, measured telerröntgenographically. A discussion of the general circulatory changes follows, but, as the final conclusions

are built up upon the assumption that in arterio-venous fistula "there is a marked increase of venous pressure," we are unable to accept them; and this the more as it seems to us certain that in Holman's case, in which the "liver did not seem enlarged," venous pressure was either normal or at the most but slightly raised; the former being the more probable. In our experience of venous blood pressure we have found no exception to the rule that any appreciable rise of general venous pressure is accompanied by easily demonstrable enlargement of the liver.

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Figs. 14-21. () Optical records of radial pulses. Time in fifths of a second. Fig. 14; Case 3 (March the 30th), arm vertical. Figs. 15 and 16; Case 4 (February the 2nd); arm horizontal and vertical, respectively. Figs. 17 and 18; Case 1 (February the 21st); arm horizontal; aneurism open and closed, respectively. Figs. 19 and 20; Case 1 (March the 3rd); patient under atropine, arm horizontal, aneurism open and closed, respectively. Fig. 21; Case 1 (March the 3rd); patient under atropine; arm vertical; the first record taken with aneurism open and the second with the aneurism closed.



Figs. 22-25. Case 1. Optical records of radial pulse: the effect of closing and opening the aneurismal sac under atropine.

Figs. 22 and 23. Twenty-two hrs. post-op., showing the effect of closing the aneurismal sac.

Figs. 24 and 25. About 48 hours post-op., the same

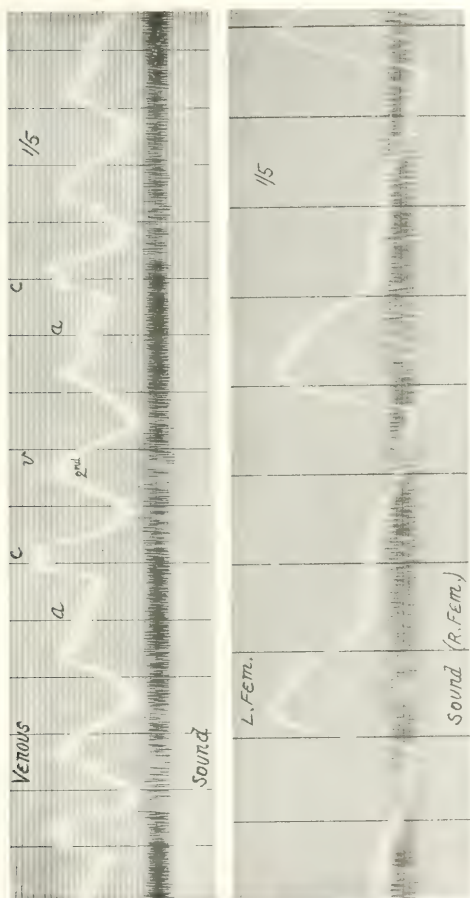
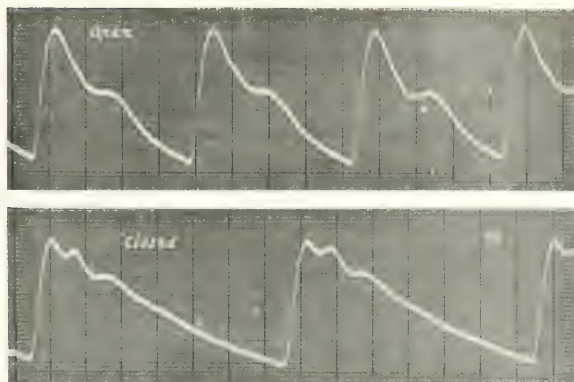
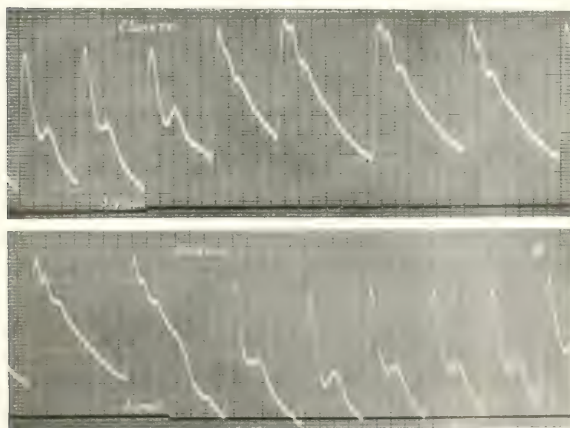


Fig. 26. Case 3 (March the 5th). Simultaneous optical venous curve from left jugular bulb and sound record from left jugular bulb, showing the relation of the curves to the waves *a*, *c* and *v*.

Fig. 27. Case 1. Simultaneous optical curve from left femoral artery and sound record over the right femoral vessel, to show the relation of the murmur to the events in the artery.



Figs. 28 and 29. *Case 2* (March the 27th). Optical radial curves (1-2) with aneurism open and closed.



Figs. 30 and 31. *Case 2* (March the 27th). Optical radial curves (3-4) after closure of the effect of closing and opening the left femoral artery.

OBSERVATIONS RELATING TO ARTERIO-VENOUS ANEURISM.

PART II.—THE IMMEDIATE EFFECTS OF AN ARTERIO-VENOUS ANASTOMOSIS ON THE DOG'S CIRCULATION.*

By THOMAS LEWIS and A. N. DRURY.

(From the Cardiac Department, University College Hospital Medical School.)

HAVING observed a number of circulatory changes consequent upon arterio-venous anastomosis in man, we thought it desirable to obtain confirmatory evidence of certain of these in animals, hoping thus to bring support to our clinical conclusions.

Method. The observations here recorded have been made upon 14 dogs (for the most part about 10 kilogrammes in weight, but sometimes larger), fully anaesthetised with morphia, paraldehyde and ether. We describe the *immediate* effect of arterio-venous aneurism: and it is to be remarked that these are not necessarily identical with the effects seen in our clinical cases, since in the latter the anastomoses are of long standing and are complicated by consecutive changes. It is also to be noted that in the present article we are dealing with animals fully under the influences of anaesthetics, and that the anaesthesia itself alters the circulatory conditions. In one respect the effect of the anaesthetics employed is particularly noticeable: they abolish entirely, or almost so, the vagal tone and natural vagal reflexes. Although from time to time acceleration of the heart's action has been manifest immediately an arterio-venous anastomosis is opened up and arterial pressures fall, and a slowing, distinct or profound, has sometimes occurred when the anastomosis is closed and arterial pressures rise (Fig. 1); these effects have been confined to the early stages of the experiments in which they have occurred, and almost always have been entirely absent at a later stage; so that in this respect the heart behaves much as does the

* Work undertaken for the Medical Research Council.

atropinised heart. As we found clinically, so we find experimentally, that this cardiac acceleration is independent of the events on the venous side, being seen from time to time in the absence of a rise of venous pressure. It is dependent upon an arterial event and is vagal in origin.

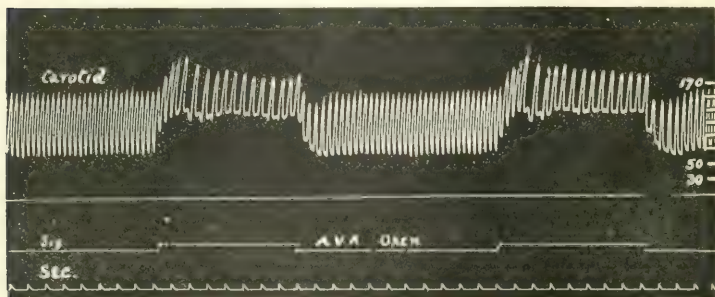


Fig. 1. Dog S.F. External iliac anastomosis; chest intact, natural respiration. Carotid arterial pressures recorded by means of Hürthle's manometer. The pressure calibration is recorded against this and subsequent arterial curves in mm. Hg.. A downstroke of the signal in this and all subsequent text figures marks the approximate position at which the anastomosis was opened; an upstroke marks the closure. Time in seconds in all text figures.

To record the *carotid pressure changes*, Hürthle's manometer has been used as a routine: this recorder allows the systolic and diastolic pressures and their changes to be gauged with sufficient accuracy. For the form of the pulse beat and its changes, Wiggers' optical recorder has been attached to the same artery. To record *venous pressures*, a wide-mouthed glass cannula has been inserted via the external jugular vein into the right innominate vein, or more commonly into the superior cava. It is connected to a citrate manometer, on which the pressure may be read in millimetres of water, or to a wide-bore manometer, to the free end of which a very light bellows recorder is attached: with the last arrangement a rise of 1 cm. of water pressure corresponds to approximately 1 cm. excursion of the lever. No venous pressure readings or curves have been accepted in which the manometer failed to oscillate with the heart beats, or in which the manometer failed, while the chest remained closed, to show an extensive movement with each respiration, natural or artificial. It has also been our habit to test the sensitivity of this manometer by pressing lightly on the abdomen: if the manometer is properly connected, very light pressure on the abdominal contents gives an almost immediate rise of venous pressure.

To estimate the influence of anastomoses upon the *flow of blood* in the arteries, Ludwig's "Stromuhr" has been used, the spare carotid artery being chosen for this purpose. Such observations have been made after the injection of 200 mgr. of Howell's "Heparin," a dose which sufficiently inhibits blood coagulation in the instrument over a period of one or more short series of observations. By a short series of observations we mean the alternate determination of flow with the anastomosis in and out of play, repeated 3 or 4 times: the average values of such observations have been accepted if individual readings have been uniform within about 10 per cent.

To estimate changes in the *output of the heart*, a glass cardiometer has been employed, after opening the chest in the middle line, a cuff of the opened pericardium being tied over the mouth of the container, in which case the volume change of the whole heart is determined; or the ventricles being inserted alone through a central hole in a rubber membrane, tied over this mouth. The cardiometer has been connected by wide bore tubing to a large but light bellows recorder.

To estimate *volume change in the intestine* a loop of the gut has been drawn into a suitable closed box, the latter being connected to the sensitive bellows recorder used for venous pressures.

To obtain an approximate idea of the amount of blood flowing through the anastomosed vessels, the anastomosed artery has been opened fully and the blood allowed to flow for 15 or 20 beats into a graduated vessel. The measure thus obtained is in excess of the arterio-venous leak, since the blood issues against atmospheric pressure, whereas, in the case of the anastomosis it flows against the pressure in the distended vein.

For the *anastomosis* itself Crile's cannulae (3 or 5 mm. bore) have been used. The advantage of such cannulae is that while free flow is obtained, this flow is through a tube lined by living endothelium throughout, and clotting does not occur at any stage of the observations. In three animals the peripheral end of the superficial femoral artery and the central end of its companion vein have been anastomosed end to end, after dividing the vessels. Actually it was found that the leak so produced was often insufficient for our purposes, and in the remaining experiments a similar end to end anastomosis of the external iliac artery and vein was used. The degree of leak so produced, in this case sometimes in excess of what was desired, could be regulated by partially obstructing the vein.

The order of procedure has been to connect up the arterial and venous pressure recorders and to prepare the anastomosis, maintaining it closed. A series of arterial and venous records have then been taken and the effect of opening the anastomosis for periods of about 15 to 20 seconds, or for longer periods, has been observed, with the dog breathing naturally. "Stromuhr" readings, volume curves of the intestine, optical arterial curves have been taken almost exclusively at this stage. Artificial respiration has then been employed, and a further series of curves taken, to compare with those under natural breathing. A fall of the arterial curve as a whole and a rise of the

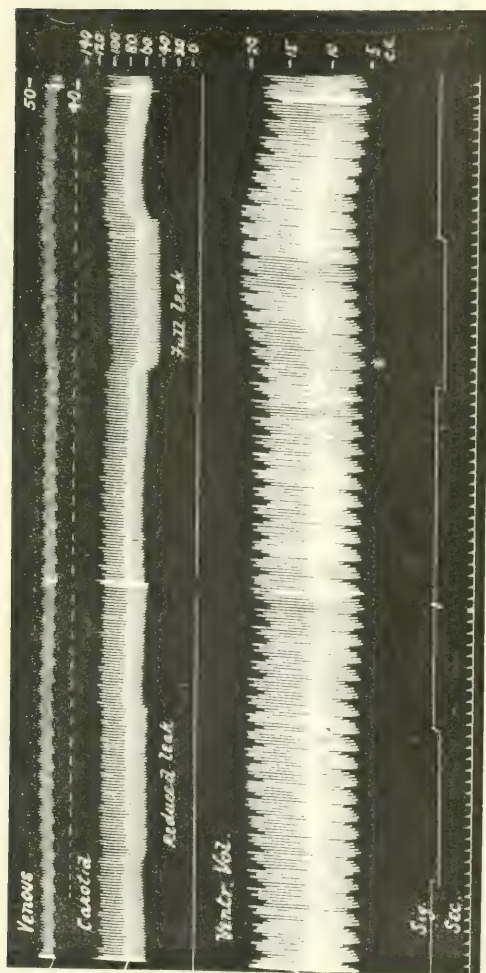


Fig. 2. Dog S. H. External iliac anastomosis; chest open, artificial respiration. Venous and arterial pressure curves, taken simultaneously with a ventricular volume curve. The calibration of this and subsequent venous curves is expressed in millimetres of water, zero level being in each instance the height of the innominate vein. The values are sometimes plus, as here, and sometimes minus. The venous curves, as in all figures, show the heart beats. The calibration of the volume curves is in cubic centimetres; systole writes downwards in these. A very small decrease in cardiac volume is marked by an asterisk.

The figure shows the effects of opening and closing the anastomosis. In the right-hand record the leak was full; in the left-hand record it was reduced. Illustrating the increased effect on arterial and venous pressure of increasing the leak; and also the close relation between venous pressure and cardiac output.

venous curve as a whole is the result ; otherwise the curves have usually shown no very serious modifications (see Table I). The chest has then been opened (8 experiments) and the cardiometer arranged to add its record of the heart's volume change. It is to be stated that the method of recording output cardiometrically, the only method available at the moment, is not beyond criticism. The opening of the chest, the employment of artificial respiration, and lastly, but not least, the fitting of the cardiometer itself, all produce changes, more or less profound, in the circulation. The results so obtained need to be judged very broadly therefore. Volume changes which are seen can hardly be regarded as constituting proof of what happens in the intact subject, but rather as indications which are to be closely controlled by such measurements of arterial and venous pressure, etc., as may be obtained without gross interference with the thorax and its contents. Thus, in their application to the clinical case, those cardiac volume changes are most reliable which are associated with substantially the same changes of arterial and venous pressure as were seen to occur previously while the chest of the animal was still intact.

Venous pressure and cardiac output.

End to end anastomosis of the superficial femoral artery and vein, while it produces the characteristic changes of arterial pressures, presently to be described in detail, is apparently without influence upon general venous pressure. When the external iliac vessels are used, the arterial pressure changes are of the same kind, though somewhat more profound, and the venous pressure may or may not change ; thus, in one such animal we found the venous pressure consistently unaltered throughout the experiment ; in two animals the venous pressure rose constantly on opening the anastomosis ; while in the remaining five experiments there was sometimes a slight rise of venous pressure, and sometimes no change. Thus, observation shows that the venous rise is as often absent as present : even when it occurs it usually amounts to but a few millimetres of water pressure ; the maximum change seen has been a rise of 9 mm. of water. A fall of pressure has not been witnessed.

The degree of the rise is related to the amount of the leak : if at the establishment of a full anastomosis the venous pressure rises a few millimetres, the venous rise can be abolished or reduced by narrowing the anastomosis, while conspicuous arterial effects are still obtained. Thus in Fig. 2, an external iliac anastomosis was opened on two occasions, as shown by the signal. On the second occasion a very appreciable fall of both systolic and diastolic pressure occurred, the last falling the more conspicuously and the pulse pressure increasing, as is the rule. Meanwhile the venous pressure increases by a few millimetres of water. On the first occasion the same anastomosis was opened, but the leak had been reduced by clamping the vein half-way across. The arterial pressures change less, the rise of venous

TABLE I.
Examples of established arterial pressures. (Chest intact.)

	Carotid pressures.				Venous pressure in mm. water on opening A.V.A.	Respiration.
	A.V.A. closed.		A.V.A. open.			
	(syst.)	(diast.)	(syst.)	(diast.)		
<i>Dog R. U.</i>	115	75	110	60	unchanged	natural
<i>Dog R. V.</i>	140	65	135	50	unchanged	natural
	90	45	90	30	unchanged	artificial
<i>Dog R. X.</i>	160	72	158	58	unchanged	natural
	140	70	134	55		artificial
<i>Dog R. Z.</i>	140	85	135	70	unchanged	natural
	130	80	125	65	rise of 3	natural
	105	60	105	45	rise of 3	artificial
	100	60	100	45	unchanged	artificial
<i>Dog S. A.</i>	160	78	180	44	rise of 2	natural
<i>Dog S. B.</i>	180	110	170	90	rise of 7	natural
	120	70	120	50	rise of 3	artificial
<i>Dog S. D.</i>	142	60	150	45	rise of 2	natural
	135	70	130	55	unchanged	natural
	135	65	130	50	rise of 2	artificial
	140	78	135	56	rise of 2	artificial
<i>Dog S. E.</i>	130	78	125	58	rise of 2.5	natural
	135	85	140	70	rise of 4	natural
	135	88	135	55	rise of 5	artificial
<i>Dog S. F.</i>	120	70	150	35	rise of 5	natural
<i>Dog S. G.</i>	160	80	160	68	unchanged	natural
	150	80	148	55	rise of 1	natural
<i>Dog S. H.</i>	130	90	125	60	unchanged	natural

In all the animals exemplified in this table the anastomosis was between the external iliac vessels.

TABLE II.
Degree of leak, and effect on venous pressure and cardiac output.

	Carotid pressures.				Venous pressure in mm. H ₂ O on opening A.V.A.	Cardiac output in cc. p. beat.		
	A.V.A. closed.		A.V.A. open.			A.V.A.		
	(syst.)	(diast.)	(syst.)	(diast.)		Closed. chest	Open. intact	
<i>Dog S. D.</i>	142 135 135	60 60 70	150 135 130	45 50 55	rise of 2 rise of 1 unchanged	" " "	" " "	full leak full leak reduced leak
<i>Dog S. F.</i>	120 120	70 70	150 130	35 50	rise of 5 rise of 2	" "	" "	full leak reduced leak
<i>Dog S. G.</i>	150 160 160 65	80 90 80 45	148 160 160 60	55 70 68 35	rise of 1 rise of 1½ unchanged unchanged	" " — 4.5	" " — 4.8	full leak full leak reduced leak full leak
<i>Dog S. H.</i>	115 115	60 60	105 110	40 48	rise of 3 rise of 1.5	8.4 9.2	10.0 10.0	full leak reduced leak

In all these experiments the anastomosis was between external iliac artery and vein.

pressure is only just distinct. In the dog the external iliac vessels, when anastomosed, yield arterial pressure changes which are closely comparable to those clinical cases of arterio-venous aneurism which we have described and in which the superficial femoral vessels communicate: and the amount of leak into the vein appears, with vessels of this calibre, to be just sufficient, or just insufficient, to produce a rise of general venous pressure. Illustrations of records showing constant and raised venous pressure, respectively, are given in Figs. 3 and 4.

Comparing the change in venous pressure with the change in cardiac output on opening the anastomosis, the usual relationship of these two phenomena is found: a rise of venous pressure increases the input into and the output from the heart: and the more the venous pressure is raised the more the output is increased. Thus in Fig. 2, with the full leak and slight rise of venous pressure, the volume curve of the ventricles shows a slight but very definite increase of output: with the reduced leak both the venous rise and the increased cardiac output are only just appreciable. Further illustrations of the relation between venous pressure and output will be found in Figs. 5 and 7. In the first of these venous pressure and output are unaltered: in the second both are increased (see also Table III). A similar relation between fall of venous pressure and fall of cardiac output is established when the anastomosis is closed: in this instance, however, another factor, presently to be described, often disturbs the relationship.

Comment. In our patients we were unable to find evidence of a rise of general venous pressure: in the two patients in whom the anastomosis could be closed, the evidence appeared to us particularly convincing. The venous measurements were taken, however, from a vein lying at some distance from the heart: and a chief object of the present investigation was to gain knowledge of the pressure changes in the venous system at a point nearer to the right auricle. Although it did not appear to us possible that any material rise of right auricular pressure could occur without a corresponding increase of the whole pressure gradient to the periphery, providing that the veins remain unobstructed, yet it was felt desirable to test further our view that an appreciable leak from artery direct to vein could occur without raising the pressure on the veins generally. Our observations upon dogs show that this is the case for anastomoses of the order considered. The same observations indicate clearly, however, that such a rise of general venous pressure would occur more frequently or with regularity in anastomoses of larger vessels.

In describing the clinical cases, we have assumed that there is no material change in the output of the heart when an arterio-venous anastomosis had been opened or closed. This assumption was based in part upon the absence of change in venous pressure. The experimental work has its importance in confirming the validity of this assumption: since it shows that in the circumstances of the case venous pressure and cardiac output

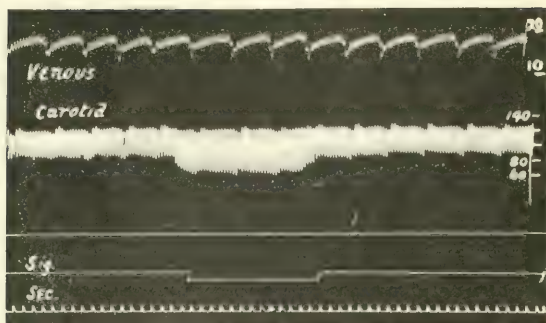


Fig. 3. Dog S.H. External iliac anastomosis; chest intact, natural breathing. Venous and carotid pressure curves. When, as here, the chest is intact, the venous curve shows conspicuously both respiratory and heart cycles. The arterial pressures change, but the venous remains constant.

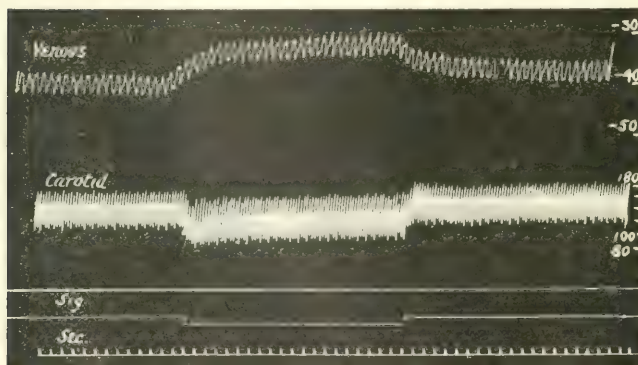


Fig. 4. Dog S.B. External iliac anastomosis; chest intact, natural breathing. Venous and carotid pressure curves. Arterial pressures change conspicuously and the venous pressure rises by about 6 mm. of water, on opening the anastomosis.

run hand in hand, and that neither the one nor the other is necessarily increased by anastomoses producing arterial changes comparable to those found in the clinical cases we have recorded.

TABLE III.
Venous rise and cardiac output.

	Carotid pressures.				Venous press. in mm. H ₂ O on opening.	Cardiac output in cc. p. beat.		Heart rate.		Dilatation of heart.
	A.V.A. closed.		A.V.A. open.			closed	open	closed	open	
	(syst.)	(diast.)	(syst.)	(diast.)						
<i>Dog R.V.</i>	50	25	44	15	unchanged	5.0	4.6	186	186	conspicuous and progressive
<i>Dog R.X.</i>	54	25	48	14	unchanged	5.8	6.2	156	162	slight
	75	40	65	25	unchanged	5.8	5.7	174	174	none
<i>Dog S.B.</i>	80	50	60	30	rise of 9	10.4	12.6	264	264	present
	110	60	60	30	rise of 3	10.3	10.9	270	264	
<i>Dog S.F.</i>	75	20	70	5	rise of 1	8.6	9.6	165	159	present
	50	20	55	5	rise of 2	6.3	8.8	192	198	conspicuous
<i>Dog S.G.</i>	65	45	60	35	unchanged	4.5	4.8	216	208	slight
<i>Dog S.H.</i>	100	40	100	30	rise of 5	13.8	15.6	216	222	little or none
	115	60	110	40	rise of 3	8.4	10.0	237	237	
	115	60	110	48	rise of 1.5	9.2	10.0	234	237	
	130	70	135	50	unchanged	13.0	13.2	216	216	

In all these experiments the anastomosis was between external iliac artery and vein.

Size of the heart.

On opening an anastomosis (the heart rate in these experiments remaining as usual unaltered), an immediate decrease in the size of heart seems to be invariable, or almost so; it usually amounts to from 1 to 2 cubic centimetres, though it may be less, and is conspicuous or not according to whether there is or is not a conspicuous fall of mean arterial pressure. The duration of this fall of volume is brief, being precisely that of the fall of blood pressure, beat for beat as nearly as can be estimated. During the period of the fall, the output of the heart may be unchanged (Fig. 5) or slightly increased. In the instances where there is increased output the fall in cardiac volume is attributable in part to this factor. Presumably the increased output is due, when it occurs, to decreased resistance in the aorta, the heart losing some of its residual blood: for the venous pressure, even when raised,* cannot materially affect output for several cardiac cycles. But the initial decrease in the size of the heart cannot always be ascribed to this cause; sometimes it is wholly due to a different cause, namely, to decrease in the size of the coronary vessels; the last

* When venous pressure rises and the whole heart is in the cardiometer, the increase in the size of the right auricle will tend to mask this initial decrease in heart's size.

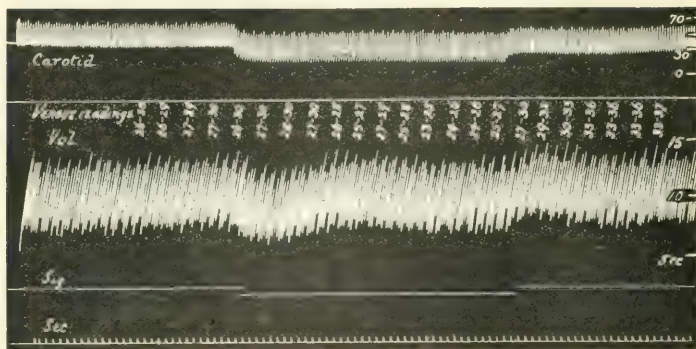


Fig. 5. (· · ·) Dog R.X. External iliac anastomosis; chest open, artificial respiration. Carotid pressure curve, venous readings and cardiac volume curve. The venous readings were taken at equal intervals over a stretch of curve of known duration, the times at which the anastomosis was opened and closed being noted; the readings have been written in subsequently at regular intervals, subdividing the curve by the number of actual readings.

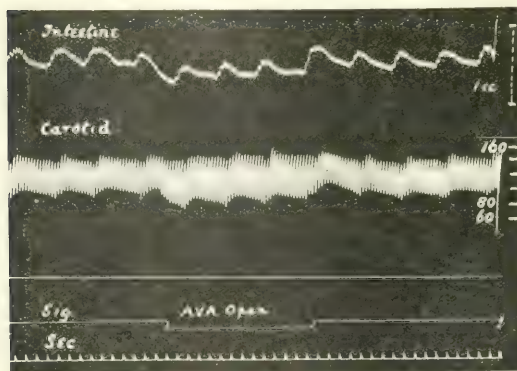


Fig. 6. Dog S.H. External iliac anastomosis; chest intact, natural breathing. Intestinal volume curve, calibrated in cubic centimetres and arterial pressure curve.

is in fact probably the chief cause of the heart's shrinkage in all instances of the initial decrease of size. As often as not the heart's output remains unchanged over this phase of falling volume; meanwhile venous pressure and input are steady or are raised. Diminution in the size of the heart cannot in these circumstances be due to change in the content of the heart's cavities. Fig. 5 may be regarded as a typical example of many of the cardiac volume

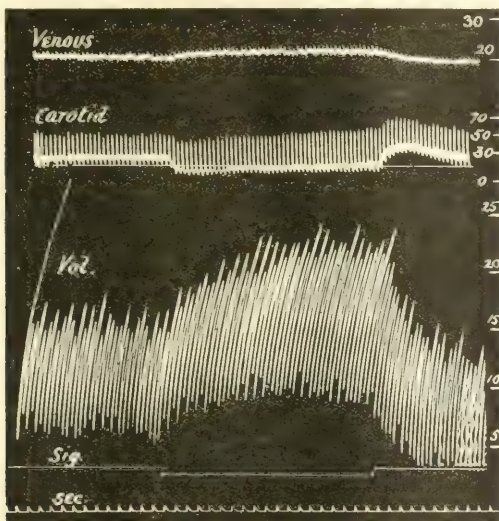


Fig. 7. Dog S.F. External iliac anastomosis; chest open, artificial respiration. Venous and carotid curves, taken simultaneously with a cardiac volume curve.

curves. In this instance arterial pressures fall conspicuously on opening an iliac anastomosis. The venous pressure remains unchanged: the output of the heart is unchanged, but the heart shows an initial decrease in size. From this there is shortly a recovery, and the curve runs straight until the anastomosis is closed, when the events are reversed. A similar initial fall of cardiac volume, unaccompanied by change of cardiac output, is shown in Fig. 8; in Fig. 7 the fall is less distinct and soon gives place to pronounced dilatation of the heart. In Fig. 2 the initial fall is exceptionally small; it is, in fact, only just perceptible.

The volume of a loop of intestine passively follows the arterial pressures (Fig. 6). A loop having approximately one-third the volume of the heart,

diminished in size by one-fifth of a cc. in an instance in which the change of arterial pressure was not conspicuous. The influence of the coronary vessels upon cardiometer curves has not been appreciated; it is obviously of moment. Dr. Fred Smith has measured, by injection, the content of the coronary vessels in several of the dogs used in these experiments. He finds in these dogs a coronary capacity of about 10 cc. at a pressure of 90 mm. Hg., and of 7.5 cc. at a pressure of 70 mm. Hg.. A fall of 10 mm. distension pressure in the coronary vessels of such hearts would reduce the volume of the heart by approximately 1 cc..

The reverse change, namely, an increase of similar degree in the size of the heart, is seen immediately on closing the anastomosis (Figs. 5 and 8); it is ascribed to filling of the coronary vessels, and in lesser degree to decreased output consequent on an increase of peripheral resistance.

A change in the size of the heart during the period intervening between the initial decrease and final increase in size discussed is the rule. It consists of a dilatation, quickly reaching and continuing at a certain level (Figs. 5 and 7) or progressing (Fig. 8). In animals in which the arterial pressures are well maintained after the chest is opened and the cardiometer fitted, little or no such dilatation is seen (Fig. 2); in animals in which the arterial pressures are low this dilatation may be conspicuous and progressive. Thus, at the stage of the experiment from which Fig. 8 was taken, the animal's condition was not good; arterial pressures were very low and the cardiac output small. On opening an iliac anastomosis the arterial pressures fell further and continued at this very low level until the anastomosis was closed again. The cardiac volume first declined sharply and then increased steadily until the anastomosis was closed, when there was a gradual return to normal. This progressive dilatation of the heart was not due to a change of venous pressure; the venous readings fluctuated over the same 3 mm. of the water column throughout the record. The dilatation is accounted for by lessened output, which the curve distinctly shows. Such a conspicuous and progressive dilatation of the heart following a few seconds after the opening of the anastomosis is not to be regarded as a healthy reaction; occurring as it does in animals in which the circulation is failing, it is attributable to lowering of the arterial pressures to an extent that the supply of blood to the coronary vessels is insufficient to nourish the heart. The heart then dilates and its output declines. That in such an experiment the heart muscle has been reduced to a hypodynamic state, first by the general conditions of the experiment and lastly by the opening of the anastomosis, is well illustrated by Fig. 8. Not only is there the progressive dilatation, a dilatation ascribable purely to lessened output and consequent increase of the heart's residual blood, but there are several other manifestations. The heart rate declines slightly during the period of the leak and extra-systoles appear, which disturb the otherwise regular heart rhythm; moreover, the pulse shows brief alternation after these extra-systoles. Extra-systoles alone or alternation

of a more conspicuous kind have been seen in other experiments of this series under very similar circumstances.

Conspicuous dilatation (5 or more cc.), which does not progress is often associated with a rise of venous pressure and an increased cardiac output (Fig. 7). In such it is difficult fully to analyse the causes of dilatation: but since such rises of venous pressure are not necessarily accompanied by dilatation other than increase in the heart's diastolic volume (as in Fig. 2, where arterial pressures run high), and since conspicuous dilatation may be seen in the absence of a venous rise (Fig. 8), we are inclined to attribute all increases of the heart's volume in our experiments primarily to defective arterial (and in particular coronary) pressures, consequent upon interference with the wall of the thorax, upon anæsthetic, etc., this defect being exaggerated by the opening of the arterio-venous anastomosis. While it has not been possible to exclude rise of venous pressure as a direct cause of dilatation in all instances, it has not appeared to be the chief factor concerned: that is so because the rise of venous pressure has never been great. Given larger anastomoses and consequently larger rises of venous pressure, this factor would no doubt play a chief rôle. Such anastomoses have been avoided, since they would have been less comparable to the clinical cases which we have recorded.

Comment. In the clinical cases no change in the diastolic size of the heart could be determined on opening or closing an anastomosis. It would have been preferable had the X-ray observations been undertaken with the patients under atropine, to eliminate changes of heart rate. We are not able to state that there was no change of diastolic volume, but only that such changes as may have occurred could not have been large. That dilatation of the heart does not necessarily occur, when an anastomosis sufficient to produce conspicuous arterial changes is opened up, is definitely indicated by our experiments. In speaking thus of dilatation, we have in mind, first of all, a dilatation occurring within the first minute, as distinct from such a slow dilatation as may be consecutive to the lesion, and such as is believed to explain chronic enlargement of the heart in clinical arterio-venous aneurism. Although in man or in an animal, in which arterial pressures are normal, a substantial lowering of these pressures may not at once result in cardiac dilatation, this dilatation will very probably follow if the lower pressures are maintained for prolonged periods of time. This question has already been discussed in the clinical section of these studies.

Our experiments suffice to demonstrate that dilatation of the heart can occur consequent upon an arterio-venous aneurism apart from increased venous pressure: and tend to indicate that a chief cause is the fall of coronary arterial pressure, a conclusion already reached from our clinical observations. Dilatation of the heart as a consequence of arterio-venous aneurism may be said to be dependent probably on two chief events. It will depend upon lowering of coronary arterial pressure on the one hand, and, arising from this

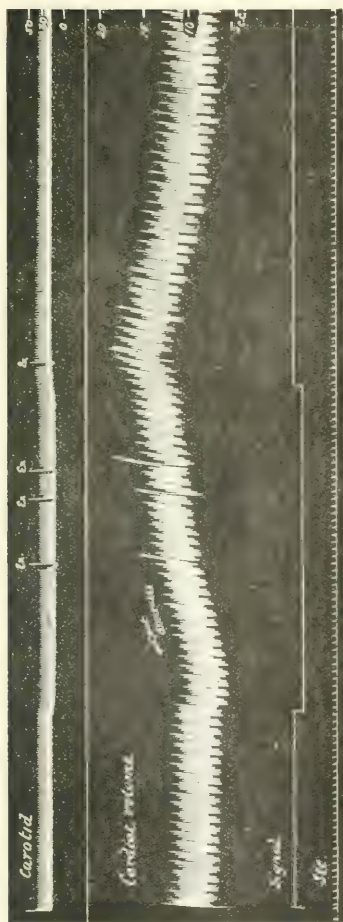


FIG. 8. (8 & 9) Dog R.V. External iliac anastomosis: chest open, artificial respiration. Carotid pressure and carotid volume curves from a dog in which the heart was in a hypodynamic state. The venous readings are not written on the curve as they were unchanged throughout, apart from a regular fluctuation of 3 mm. with the heart beat. *Ca*, extra-systoles.

cause, it will be more conspicuous the lower the arterial pressures are originally and the more these pressures are affected by the leak. It will probably also depend, when the leak is sufficient appreciably to raise general venous pressure, upon this rise of pressure, the heart dilating to accommodate the additional blood flowing into it.

Changes in arterial pressure described in detail.

The immediate effect of opening an anastomosis. between vessels of the size of the external iliacs, on the diastolic pressure is invariable. This pressure falls precipitately by 15 to 30 or more mm. Hg. The systolic pressure shows less constant change: usually it falls precipitately by a few millimetres: in some instances the fall is greater, but it never equals in amount the fall in diastolic pressure (Figs. 4, 5, etc.): the pulse pressure invariably increases. In some instances there is little or no change of systolic pressure (Fig. 6), or an actual rise amounting exceptionally to 20 or 30 mm. Hg.: in the last instances, the diastolic pressure falling as usual, the highest pulse pressures are seen.

Pressures established after opening an anastomosis. In general these are similar to those prevailing a few seconds after the actual release of the anastomosis, though both systolic and diastolic pressure, but especially the systolic, usually rise a little: that is to say, there is usually a little recovery in the pressures within a few seconds of the establishment of the leak (see Figs. 4 and 9). Thus the established diastolic pressure is usually 15 to 20 mm. Hg. below normal. Recovery may not occur, in which case the tracing is of the forms shown in Figs. 3 and 5, consisting of straight lines. Such flat curves are rarely, if ever, associated with a change of venous pressure or of cardiac output, and are closely comparable to those we have seen clinically.

In other instances the recovery is spread over a more considerable period of time, namely, 20 or 30 seconds (Figs. 9 and 10). This recovery and its variation makes it difficult to express the pressures prevailing in tabular form.

When, as a result of opening an anastomosis, a rise of systolic pressure above normal occurs immediately or during the subsequent recovery (Figs. 9 and 10), the venous pressure is invariably found to be increased and so also is the cardiac output: to this increase of cardiac output the higher systolic pressure is mainly attributed. The two phenomena, namely, change of systolic pressure and change of venous pressure, do not run quite parallel, however: for a rise of venous pressure may be and often is associated with a fall of systolic pressure. Two factors, the direct effect of the leak tending to lower systolic pressure, and the indirect effect of raised venous pressure, when this occurs, tending to raise systolic pressure by increasing cardiac output, are often in conflict.

While it is true that the greater the leak the greater is the fall of diastolic pressure; and while it is also true in general that the greater the leak the

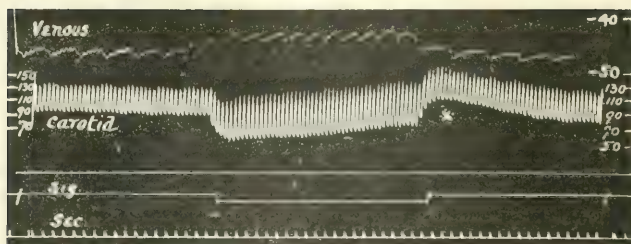


Fig. 9. Dog S.E. External iliac anastomosis; chest intact, natural breathing. Venous and carotid pressure curves. Illustrating recovery of arterial pressures, in the period during which the anastomosis remained open.

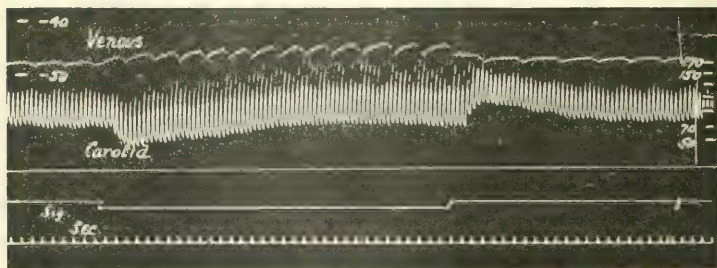


Fig. 10. From the same animal and under similar conditions. Venous and carotid pressure curves, illustrating an unusual recovery of arterial pressures and a progressively increasing venous pressure in the period during which the anastomosis remained open.

more likely is there to be a rise of venous pressure; yet because these relationships are not precise, a further relationship between fall of diastolic pressure and change in venous pressure is not always to be established, though it may exist. Presumably the absence of a fixed relationship of this kind is due (as the absence of a similar relationship in the case of the systolic pressure) to the diastolic pressure being often influenced in opposite directions, there being on the one hand the tendency for the leak directly to reduce it, while a rise of venous pressure tends, by increasing cardiac output, to increase it.

The explanation of the recovery of mean pressure when this occurs shortly after the anastomosis becomes established is quite clear. It is always accompanied by an increase of cardiac output (Fig. 7); the rate

and degree of recovery and the rate and degree of increase in cardiac output run precisely hand in hand. It is also evident that the increased cardiac output at this stage is controlled by venous pressure. The increased cardiac output does not occur unless venous pressure is raised. Usually the venous pressure rises quickly and forms a plateau; in this circumstance the output increases quickly and remains constant, or it may show a more gradual increase. In the rarer instances when the venous pressure continues to rise, the cardiac output increases *pari passu*, and the recovery of arterial pressures is very conspicuous. Thus, in Fig. 10, the gradual ascent of venous pressure is manifest and is associated with a rise of systolic pressure to a point well above normal. In Figs. 7 and 9 the venous curve is more of the plateau form, though careful measurement shows venous pressure to be rising a little throughout.

Effects of closing an anastomosis. These effects are naturally in general opposite to the effects of opening an anastomosis; sooner or later the pressures return to normal. The form of curve is, however, influenced by previous events. In instances where the arterial curve is flat over the period during which the anastomosis is open (Fig. 3), the pressures usually return to normal promptly. In instances where there has been a previous recovery of arterial pressures, these rise above normal when the anastomosis is closed (Figs. 7 and 9), and subsequently fall away to normal. This rise in the general level of the curve above normal is associated with a cardiac output in excess of normal and with a decline of the raised venous pressure to normal. As the last event does not occur in a constant time interval, the rise of general level may be transient or it may be spread over many heart beats (see 2nd curve of Fig. 2).

There is, however, a further factor which complicates the curves of closures. Over the period during which the anastomosis is open, the ventricles sometimes dilate: they return to their normal volume when the anastomosis is closed. The blood, which has collected in the heart, is thrown into the arterial system and the rise of arterial pressures which occurs on closure may be thus exaggerated. That this factor may play its part is shown by instances in which a rise of arterial pressures above normal occurs on closing the anastomosis even though venous pressure has remained constant. A rise above normal does not occur unless there has been either a rise of venous pressure or some degree of cardiac dilatation (or both) over the period of leakage. A rise of arterial pressures above normal seems always apparent if there has been dilatation, whether venous pressure has been raised or not, unless the dilatation passes off very gradually. Clearly, the rate at which the dilatation passes off will influence the extent of the subsequent rise of arterial pressure. In a few instances the pressures do not rise to normal for some while after the anastomosis is closed (Fig. 5): in such the output of the heart is found to be decreased and the venous pressure to rise a little when the anastomosis is closed.

It is not certain how this comes about, though we are inclined to the following view. In the period during which the anastomosis is open, the heart is under-nourished, but is still just able to drive out the unchanged volume of blood delivered to it by the veins, since it drives out this blood against a reduced assistance. When the anastomosis is closed, the muscle of the heart takes some while to recover strength, and during this period its output is below normal, because the resistance it has to overcome has risen.

Comment. In our clinical cases we have found both the systolic and diastolic pressures lower than normal and the pulse pressure increased. This was to have been anticipated on theoretical grounds and from a comparison with aortic regurgitation. We have also found that on compressing the vessel leading to the anastomosis, both pressures rise, but that the diastolic pressure rises more than does the systolic: both rise in fact to normal levels, and the pulse pressure becomes normal. It is to be pointed out, however, that, while the systolic pressure in man, by general consent, is obtainable with considerable accuracy, there is more doubt as to the value of diastolic readings, and not all observers accept the commencing decline of the Kurotkow sounds, in the artery beyond the cuff, as yielding a true value. Whether it actually represents diastolic pressure or not is in more doubt than that it represents some critical pressure not varying greatly from the diastolic; so that even if the clinical readings are not accurate expressions of diastolic pressure they are almost certainly valuable in judging the relative values of the lowest pressure ranges of the pulse, while comparing one case and another, and *a fortiori* while comparing these lowest pressure in the same case from time to time. Hürthle manometer and optical arterial records (Figs. 11 and 12) from dogs place the changes in the arterial pressures, when an arterio-venous anastomosis is opened or closed, beyond doubt; and as those readings of systolic and diastolic pressure, which we previously obtained from patients, are of the same kind and order, we have no hesitation in believing that they are accurate, at all events in this relative sense.

It has been seen that in dogs the types of arterial curve on opening and closing an anastomosis, though constant so far as the main events are concerned, are very varied in their detail. The type to which the clinical cases have conformed is that in which, after a steep fall of pressures these remain constant until the closure, when the return to normal is prompt; a recovery of arterial pressures during the period following release of an arterio-venous anastomosis has not been observed. The clinical type of curve is found experimentally when there is no rise of venous pressure and no increase of cardiac output: an observation which harmonises with the absence of venous change in our patients and with our view that cardiac output was unaltered.

In our clinical cases, however, a slight and very transient rise of systolic pressure above normal was obtained on closing the anastomosis. In experiments in which a similar event has been seen, it has been shown to be due

either to a transference of venous blood, as the venous pressure falls, or to a transference of cardiac blood, as dilatation of the heart passes away to the arteries. The rise of systolic pressure in the patients has been small in the case of the brachial artery, greater in the case of the popliteal, to which a special explanation applies. In the patients it is due in some part to the associated fall of cardiac rate (maximal at this phase) and to an accompanying increase of pulse pressure, a factor not present in our animals. It might be attributed solely to change of heart rate were it not that a similar though lesser rise was observed in one patient under atropine: this rise was one of but a few mm. Hg., and was maintained for only a few beats. As no pertinent change of venous pressure could be detected in this case, this small and transient rise of systolic pressure above normal can be attributed only to a slight decline in the size of the heart, and to an associated slight and transient increase of cardiac output, immediately on closing the anastomosis. In our X-ray examination of this patient we were unable to detect any reduction in the size of the heart which might not be attributed reasonably to more complete systoles, consequent upon the diminished rate of beating. This little supernormal phase of systolic arterial pressure suggests, nevertheless, that a little shrinkage of volume, diastolic as well as systolic, actually occurred, though we were unable to detect it. That the change was trivial is shown not only by the slightness of the rise of systolic pressure, but also by our inability to recognise a transient increase in the flow of blood to the limbs immediately after closing the anastomosis.

Blood flow in carotid artery and nutrition of the heart.

The blood flow in the carotid artery falls away conspicuously when the arterio-venous anastomosis is opened; it rises when the anastomosis is closed. These are the natural and anticipated results of fall and rise of mean arterial pressure. It happens that in all the experiments in which "Stromuhr" readings were taken, at the time of these observations the opening of the anastomosis was followed by a rise of venous pressure. In all but one experiment the readings were taken while the chest of the animal was intact and the animal, therefore, in good condition. In view of the rise of venous pressure in these animals, an increased cardiac output may also be assumed. In the one experiment in which the chest was open, the ventricular output was also estimated; on opening the anastomosis the carotid outflow fell from 32.7 to 24 cc. per minute;* the heart rate remained unaltered, the venous pressure rose 2.5 mm., the systolic arterial pressure fell from 110 to 100 and the diastolic pressure from 60 to 40; the cardiac output rose from 12.4 to 15.2 cc. per beat.

When an anastomosis of the external iliac vessels is closed, the chest wall being intact, the blood flow is increased in the carotid artery by percentages varying from 24 to 52 per cent..

* The carotid flow in animals in which the chest is open is usually about half the normal.

TABLE IV.

Carotid blood flow, etc. (chest intact).

Dog.	Arterio-venous anastomosis closed.						Arterio-venous anastomosis open.					
	Heart* rate.	B. P.		Venous in mm. H ₂ O	Carotid flow in cc. p. min.	Resp. rate.	Heart rate	B. P.		Venous in mm. H ₂ O	Carotid flow in cc. p. min.	Resp. rate.
		(syst.)	(diast.)					(syst.)	(diast.)			
<i>S. A.</i>	210	160	78	18	72	34.2	210	180	44	20	57	38.4
<i>S. D.</i>	138	138	78	—21.5	45	27.0	138	138	55	—18.5	35	30.0
<i>S. E.</i>	141	135	75	—52.5	109	13.5	141	150	70	—50	89	15.9
	135	140	85	—34	79	artif.	138	150	65	—27	55	artif.
	132	130	85	—58.5	73	21.0	138	135	70	—55	48	31.8
<i>S. F.</i>	208	145	90	32	77	14.1	204	150	50	—25	57	15.0
	180	120	70	—24	48	14.1	183	160	40	—19	37	15.3

* The data, other than the carotid flow values, are from simultaneous records, taken immediately before and after each set of "Stromuhr" readings.

In all these experiments the anastomosis was between external iliac artery and vein.

The change in blood flow through the carotid may be taken as an indication of changed blood flow in the arteries of the body generally; and changes of at least this order may be assumed to occur in the coronary vessels. It is to diminished flow of blood to the nutrient vessels of the heart that we ascribe certain manifestations of arterio-venous anastomosis, the lessened blood flow tending to reduce the heart to a relatively hypodynamic state.

Comment. In two clinical cases the flow of blood to the limbs was estimated with an arterio-venous aneurism open and closed. In these cases the measured flow on closing the vessel was estimated at approximately 30 and 100 per cent., respectively. The last percentage increase has not been approached in our experiments, an increase of 52 per cent. being the highest recorded.

The two series are not strictly comparable, since in the experiments the closure of the anastomosis, decreasing as it actually did the output from the heart, would tend to decrease the flow through the arteries.

The chief value of our figures from the clinical standpoint is that they indicate how large an effect on blood flow anastomosis of vessels of the order used may exert.

Respiratory rate, etc.

The opening of an anastomosis has produced in many experiments a slight but definite increase of respiratory rate, amounting to from 1 to 4 respirations per minute; in one experiment this effect was more decided,

the rate rising from 21 to 32 per minute. In other experiments there has been little or actually no change. Quickening of respiration may be accompanied by unaltered, slightly increased, or more rarely by diminished excursion. It is not uncommon to see a single and unusually deep inspiration soon after the opening of an anastomosis. The rate of inspiration and changes which occur in it are displayed by the venous curves. Thus in Figs. 2 and 3 there is no change of rate, while in Figs. 9 and 10 it is very decided.

In our clinical cases there was either no change in respiratory rate or a slight decrease on opening the anastomosis; considering simply the fact that opening enables fully aerated blood to reach the veins directly from the arteries, a decreased ventilation on opening the anastomosis would be anticipated. As has been pointed out, however, this influence is counteracted by diminution of the blood flow to the brain, sometimes completely counteracted, sometimes almost counteracted. In the experiment on dogs the instances where respiratory rate showed no change are comparable to the clinical observation. The instances in which the respiratory rate increased on opening the anastomosis are not comparable; for although a diminished supply of arterial blood to the brain would tend in this direction, and this diminution occurred, yet actually it was not so conspicuous as we believe it to have been in our patient.

The difference in behaviour is possibly to be accounted for by the fact that venous pressure was not infrequently raised by opening an anastomosis in the dog; and support is given to this view by the observation that the change of respiratory rate was greatest in animals in which the more conspicuous rises of venous pressure were seen. It is also to be stated that prolonged compression, as opposed to temporary obliteration of the femoral artery, was associated in our patient with some discomfort, which might in itself raise respiratory rate. In view of these considerations the apparent discrepancy between clinical and experimental findings does not seem important.

Form of arterial pulse.

The main changes described as occurring in the arterial pulse form of patients, when an arterio-venous anastomosis is opened up or closed, have been confirmed in the present experiments. When the anastomosis is opened (Fig. 11), the pulse becomes exaggerated in amplitude; the upstroke of the pulse becomes steeper, both half-way point and summit being reached after shorter time intervals. The pulse becomes of a less sustained form, the second wave occupying a lower place on the downstroke than formerly. The downstroke of the pulse both before and after the dirotic notch is quicker. These changes are illustrated by Fig. 11 and the following measurements (from two curves of Dog R. U.).

Heart rate.	A.V. A. open.		Heart rate.	A.V. A. closed.	
	Begin. of upstroke to $\frac{1}{2}$ -way pt.	Begin. of upstroke to summit.		Begin of upstroke to $\frac{1}{2}$ -way pt.	Begin. of upstroke to summit.
196	0.021	0.044	196	0.030	0.068
220	0.019	0.048	220	0.024	0.057

Precisely opposite changes occur when the anastomosis is closed, the change in each case beginning at the next heart beat (Fig. 12). The reasons for these changes have been discussed fully in the clinical section of our reports.

Capillary pulsation.

In several experiments we have examined the tongue and lips of the dog to see if, when the anastomosis is open and the pulse pressure large, capillary pulsation appears in the mucous membrane. None has been seen. We are not aware that capillary pulsation occurs in dogs as a result of long-established aortic regurgitation or arterio-venous anastomosis; if it does do so, our negative findings in the present experiments would confirm the view, which we have already expressed, that it is due to a consecutive change in the circulation and is not exclusively dependent upon the pulse pressure.

Amount of leakage.

To obtain a very approximate idea of the amount of blood flowing through the anastomosis between external iliac artery and vein, the anastomosed artery has been cut across at the end of several experiments, and the blood allowed to flow for 15 or 20 counted beats into a graduated vessel. The amount escaping per heart beat may then be compared with the output of the left ventricle ($\frac{1}{2}$ the output of the two ventricles) recorded at the end of the same experiment.

Dog.	Output of left ventricle in cc. per beat.	Output from cut artery in cc. per beat.	Arterial pressures.	
			(syst.)	(diast.)
R.S.	2.2	1.0	pressures low, heart alternating	
R.X.	2.7	2.0	55	30
S.B.	5.0	1.4	60	30
S.H.	6.2	1.45	110	60

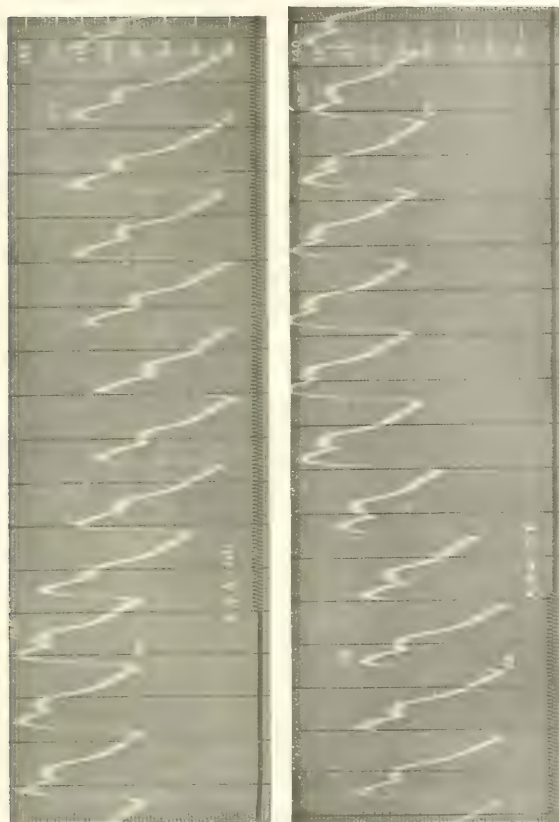
The measures thus obtained are, of course, in excess of the leak through the anastomosis, since in the first circumstances the blood issues against

atmospheric pressure, whereas, in the last it flows against the pressure in the distended vein. They serve, however, to show how rapidly blood escapes from an artery when the natural peripheral resistance has been secured; and have been utilised in discussing the amount of leakage occurring in clinical cases, in the first part of these reports.

SUMMARY.

A series of experiments upon dogs is described, in which the effects of arterio-venous anastomosis of the superficial femoral, or external iliac, vessels upon arterial and venous pressures, cardiac output, and blood flow in the arteries, etc., has been studied.

It has been found that anastomosis of this order produce changes very similar to those seen in the clinical cases of superficial femoral arterio-venous aneurisms, previously recorded (Part I); and the main conclusions of the clinical studies have been confirmed.



FIGS. 11 AND 12 (continued). *Fig. 11, L.* Optical records of the internal pressures in the carotid artery, catheterized by one of us, illustrating the effects on pressures and pulse form of opening and closing an external iliac anastomosis. The systolic and diastolic pressures of certain beats are marked on the traces. *Time in left column = 1 sec.*

SOME OBSERVATIONS ON THE EFFECTS OF HEAT AND COLD
ON THE VENTRICLES AND THE *T* DEFLECTION OF
THE ELECTROCARDIOGRAM.*

By FRED. M. SMITH, M.D. (Chicago).

(*Cardiac Department, University College Hospital Medical School, London.*)

THE *T* wave of the electrocardiogram is generally believed to be produced by the retreat of the excitation wave in the ventricles. This conception is supported by observations on a sample strip of muscle where the passage of the excitation wave produces two deflections, one corresponding to the stage of invasion and the other that of the retreat. Furthermore, the end deflection which has been attributed to the retreat of the excitation process is not confined to somatic muscle, but is common to cardiac muscle.¹ The above conception is further borne out by observation¹ on the toad's heart, in which the spread of the excitation wave is first down the *A-V* funnel to the middle of the simple ventricle and subsequently downward to the apex and upward to the base. In the electrocardiogram the *T* wave is nearly always opposite to that of the preceding ventricular deflection. The direction of the final ventricular deflection is thus apparently definitely related to the spread of the excitation wave.

Wilson and Herrmann² have more recently made further important contributions to the prevailing conception of the *T* deflection. They observed that the various areas of the ventricular surfaces pass out of the refractory state in the order in which they are known to become activated.³ The application of ethyl chloride to the ventricular surfaces modifies the direction assumed by *T* and prolongs the refractory period of the area cooled without altering the form of the *QRS* group. They further studied the changes in the *T* wave and that of the initial deflections by producing various transitional stages between the levo- and dextrocardiogram. In each instance the changes in the form of the end deflection was associated with definite alterations in the *QRS* group. They concluded from these combined observations that the final ventricular deflection is produced by the retreat of the excitation process.

* Observations undertaken on behalf of the Medical Research Council.

On the basis of the above observations, especially those concerning the order of the de-activation of the ventricles, it would seem that the application of heat and cold to various areas of the ventricles might further be employed in testing the prevailing conception of the *T* deflection. If the ventricles are de-activated in the order in which they are activated, and if heat shortens and cold prolongs the period of activation, heat and cold should furnish a satisfactory means of determining the rôle played by different parts of the ventricles in the formation of the final ventricular wave of the electrocardiogram.

It is generally known that heat and cold conspicuously alter the direction assumed by the *T* deflection^{2, 4, 5, 6 and 7}. In most instances, however, no means has been devised to confine the heating and cooling to localised areas of the heart. Frequently ethyl chloride has been employed^{2, 6 and 7}, and, as pointed out by Wilson and Hermann², it is impossible to restrict its action to definite and small areas. Furthermore, these investigators were not certain that it might not have actions other than those of cooling. Lewis¹ considers that the freezing of the surface of the ventricle with ethyl chloride throws areas of the musculature out of action. This view is supported by the fact that the freezing of the surface of the left ventricle with ethyl chloride produces a far greater downward deflection of *T* than that following ordinary cooling, and resembles that resulting from an infarction of the corresponding areas by the ligation of the coronary arteries, where muscle is known to be thrown out of action⁷.

In the following investigations* various areas of the anterior surfaces of the ventricles were heated or cooled by allowing water ranging in temperature from 12 to 40°C. to run through a thin rubber bag which was held in place over the desired area of the heart by clamps adjusted to the inflow and outflow tubes. The bag covered an approximate area of 12 square centimetres. Simultaneous curves were taken, after the heat and cold were applied to selected areas of the ventricles, from lead *II* and from a direct lead from the heart. For the latter, non-polarized electrodes were employed, one contact being placed on the area heated or cooled and the other on the right chest wall. The various areas were heated or cooled for a period of 2 to 5 minutes before the curves were taken.

The application of cold to different areas of the anterior surface of the left ventricle changed the *T* in lead *II* to a negative deflection, whereas in the direct lead the final deflection was changed from a downward to an upright phase (Fig. 1). It is to be noted that the changes in the direct lead were far greater than in that of the normal lead *II*. The alteration in the final deflection was greater in cooling the apical region of the left ventricle and less over the basal portion. In this connection it may be added that it is impossible to cool or heat an area of any appreciable size over the base of

* Eight dogs were used in the investigations. They were fully anaesthetised with morphia, paraldehyde and ether.

the left ventricle without cooling or heating the vessels coming down from the circumflex branch of the left coronary artery. Under these circumstances the effect of cooling or heating is not necessarily localised to the point of application but may extend apexwards; the corresponding changes in the electrocardiogram may not be attributable solely to basal cooling or heating.

The application of heat and cold to the right ventricle had the opposite effect but in lesser degree than that produced by the same agents on the left ventricle. The *T* in lead *II* was made more upright by cold and changed to a very slight negative deflection by heat. Here, again, the greatest changes were produced in the curves from the direct lead.

The curves were measured by means of the comparator. Readings of the *R* to intrinsic interval, and of the interval between the intrinsic deflection and the end of the final deflection of the direct lead (Table I). The former estimations were made to determine whether there was any change in the time at which the excitation wave reached the surface of the area cooled or heated. The latter readings were taken to determine whether the changes in the *T* deflection were associated with local changes in the length of systole. It will be noted that there was no appreciable difference in the time at which the selected area of the heart became activated as compared to the activation of the heart as a whole. It will further be seen that the changes in the electrogram on cooling were associated with a prolongation, whereas on heating they were associated with shortening of the systole, as determined by measurements on curves taken by the direct lead. In order to prove that the effects observed in the direct lead were confined to the local area, control curves were taken with the electrode on the heart outside the area cooled and heated. In these the form of the curves was unaffected, the *R* to intrinsic intervals remained constant and the electrical length of systolic was not altered by the change from hot to cold.

In two experiments* the refractory period of the apical region of the left ventricle was determined after the application of heat and cold. The method† employed was the same as that used by Lewis, Drury and Bulger⁸ in determining the refractory period of the auricles. The result (Table II) above the horizontal line represent the time intervals at which responses were obtained to make and break shocks. Those below the line indicate the time at which there was no response to the break shocks. It is to be noted that in each instance the refractory period was reduced by heat and prolonged by cold. The percentage reduction and prolongation of the refractory period correspond fairly well in the two experiments. The refractory period was reduced by heat 20 and 12 per cent., respectively, and

* I wish to express my indebtedness to Dr. A. N. Drury for his assistance in these two experiments.

† The strength of the testing shocks were about ten times above threshold value. Because of the difference in the strength between the make and break shocks, responses to the former are alone included in the table.

extended by cold in the first 50 per cent., and in the second, 40 per cent. above the normal.

The changes in the *T* deflection of the electrocardiogram following the application of heat and cold to the various areas on the anterior surface of the ventricles is associated with and apparently dependent upon a local change in the duration of the excitation process. Locally, heat shortens and cold prolongs the electrical length of systole and likewise shortens and prolongs the refractory period. These findings furnish additional evidence favouring the view that the *T* deflection represents the retreat of the excitation process in the ventricle. It may be further recalled that the changes in *T*, following the application of heat and cold to the left ventricle, were the opposite to those produced by these agents on the right ventricle. These results further substantiate the conception that the end deflection is a composite of two opposing forces in which the predominating effect of the right ventricle on the deflection is upward whereas that of the left is downward.

TABLE 1.

Dog.	No. of record.	Area of cardiac muscle cooled and heated.	Temperature.	<i>R</i> to intrinsic interval in secs.	Length of systole in sec. (electrical).	Cardiac rate.	Remarks.
<i>R.Q.</i>	6	Apex of left vent.	16°	0.009	0.269	160	
	7	" " "	36°	0.011	0.225	160	
<i>R.R.</i>	1	" " "	37°	0.007	0.192	160	
	2	" " "	16°	0.009	0.244	160	
	3	" " "	32°	0.006	0.197	158	
	4	" " "	16°	0.009	0.241	158	
	6	" " "	16°	0.009	0.197	158	Control.
	7	" " "	37°	0.009	0.196	158	"
<i>R.T.</i>	5	" " "	39°	0.009	0.198	190	
	6	" " "	17°	0.002	0.240	190	
	7	" " "	37°	0.004	0.185	180	Control.
	8	" " "	15°	0.001	0.180	180	"
<i>R.W.</i>	5	Middle of right vent.	15°	0.001	0.229	185	
	3	" " "	41°	0.001	0.192	185	
	11	Apex of left vent.	39°	0.003	0.176	170	
	13	" " "	14°	0.004	0.189	170	
	17	Base of left vent.	39°	0.001	0.220	130	
	18	" " "	13°	0.000	0.252	130	
<i>R.Y.</i>	2	Middle of right vent.	40°	0.003	0.180	180	
	3	" " "	14°	0.009	0.234	180	
	5	" " "	13°	0.002	0.160	220	Control.
	6	" " "	38°	0.002	0.160	220	"
	10	Apex of left vent.	13°	0.011	0.220	180	
	11	" " "	40°	0.009	0.172	180	
	14	Base of left vent.	41°	0.003	0.204	145	
	15	" " "	14°	0.004	0.280	145	
<i>S.B.</i>	2	Middle of right vent.	7.5	0.003	—	168	The end of <i>T</i> could not be determined.
	3	" " "	47°	0.002	0.208	168	
	4	" " "	47°	0.009	0.190	168	Control.
	6	" " "	9°	0.010	0.190	168	"
<i>S.C.</i>	8	Apex of left vent.	12.5°	0.004	0.235	188	
	9	" " "	40°	0.004	0.181	188	

TABLE II.
*Refractory period of the ventricles.**

Dog	S.C.				S.I.	
Ventricular rate ...	188	188	188	220	220	220
	Normal.	Temp. 41°C.	Temp. 13°C.	Normal.	Temp. 41°C.	Temp. 13°C.
Responses	0·176 m	0·140 m	0·244 b	0·134 m	0·116 b	0·203 b
	0·169 m	0·125 b	0·244 b	0·124 m	0·106 b	0·196 b
	0·150	0·124 b	0·223 b	0·116 m	0·102 b	0·178 m
	0·142 m	0·118 m	0·217 b	0·115 b	0·100 b	0·177 b
				0·108 m	0·096 b	0·176 m
No response	0·139 b	0·110 b	0·212 b	0·106 b	0·093 b	0·165 b
	0·119 b	0·106 b	0·188 b	0·102 b	0·085 b	0·163 b
	0·118 b	0·105 b	0·180 b	0·089 b	0·077 b	0·159 b
	0·116 b	0·086 b	—	0·080 b	—	0·145 b
Absolutely refractory period	0·141	0·114	0·214	0·107	0·094	0·170

* In these two experiments sufficient atropin sulphate was administered to completely paralyse the vagus. m—make and b—break shock.

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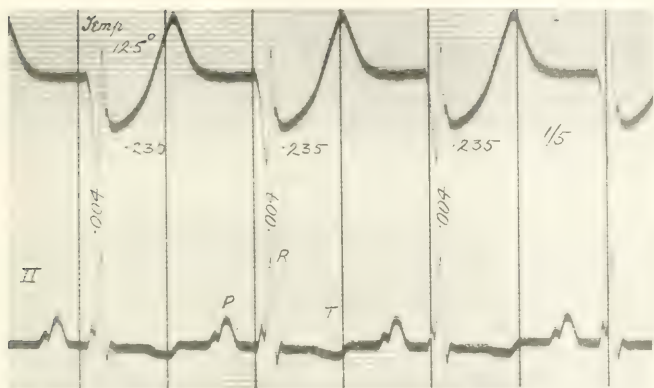


FIG. 1. Dog S.C. (record 8). Top plate 8. Apex of left ventricle cooled to 12.5° . The T wave is a negative phase in lead II and an upright deflection in the direct lead. The R to intrinsic interval is 0.004 of a second, and the intrinsic to end of T interval in the direct lead 0.235 of a second.

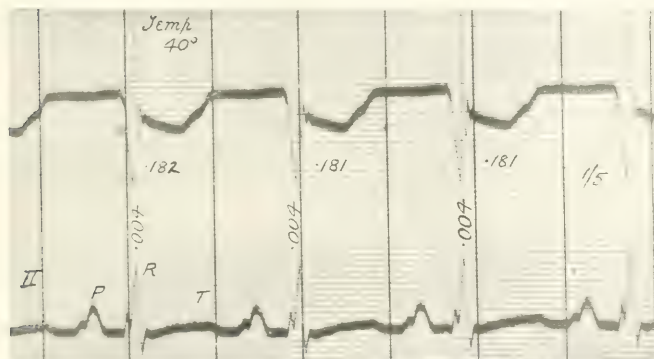


FIG. 2. Dog S.C. (record 9). Apex of left ventricle heated to 40° . The T wave is a positive phase in lead II and a negative deflection in the direct lead. The R to intrinsic interval is 0.004 of a second and intrinsic to end of T interval in the direct lead, 0.182 of a second.

ON THE CONTRACTION OF THE BRANCHES AND TERMINAL
RAMIFICATIONS OF THE AURICULO-VENTRICULAR
BUNDLE IN THE HEART.*

By MAKOTO ISHIHARA and SEISAKU NOMURA.

(From the Physiological Institute of the Imperial Kyushu University,
Fukuoka, Japan.)

It is well known that the His bundle and its processes serve to conduct stimuli to the ventricle, but the manner in which this conduction occurs has not been clear. The two branches of the His bundle ramify in order to pass finally in the form of Purkinje fibres into the proper cardiac muscle cells. Some of the longer free branches connect two opposite points on the wall of the ventricle, or the latter with the papillary muscles, but most of the shorter ones run in various directions, bridging gaps between the trabeculae of the ventricular wall. All these free branches may be designated "spurious tendons" (*pseudo fibrae tendineae*)^{1, 6 and 7}. We have been able to show that these spurious tendons can contract in response to conducted stimuli, and that they can also initiate contractions. The experiments on which these conclusions rest are outlined below. It is here to be stated that in all experiments a histological examination of the tissues, or portions of tissue, studied was undertaken by serial sections.

1st series of experiments. The isolated heart of a dog, perfused with oxygenated Locke's solution continues beating regularly while the body temperature is maintained. By cutting firmly and carefully through the wall in a longitudinal direction, the cavity of one ventricle is opened without, as a rule, influencing the normal heart beat, and thus a spurious tendon can be observed directly under a microscope of low power. It is then seen that all, both long and short, contract rhythmically with the heart beat. This rhythmical contraction can be more easily and clearly observed if the pressure of the perfusion is considerably reduced, in consequence of which the two ventricles become quiescent, while the auricles continue to beat regularly.

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In this case the spurious tendons contract with the same rhythm as the auricles. When the perfusion is stopped entirely and the auricles are thus brought to apparent rest, it is seen that the region of the sinus continues to beat for some time, and that the spurious tendons continue to contract with the same rhythm as the sinus. All these observations can be made equally well in the rabbit's and cat's heart. An example of an experiment with a dog's heart is given.

Dog, weighing 12 kg.. The temperature of the perfusion liquid and in the perfusion apparatus was 38.5 C°. The left ventricle was opened and a spurious tendon observed directly under the microscope.

Time after introduction of heart into apparatus.		Press. of perfusion liquid in mm. Hg..	Frequency per min.		
Hrs.	Mins.		Auricle.	Ventricle.	Spurious tendons.
—	0	90	82 regular	82 regular	82 regular
—	10	90	84 ..	84 ..	84 ..
—	20	90	84 ..	84 ..	84 ..
—	30	90	84 ..	84 ..	84 ..
—	40	15	87 ..	cessation	87 ..
—	50	15	87 ..	"	87 ..
1	0	15	90 ..	"	90 ..
1	10	15	95 ..	"	95 ..
1	20	95	101 ..	101 regular	101 ..
1	30	95	105 irregular	105 irregular	105 irregular
1	40	95	110 ..	110 ..	110 ..

A few of these spurious tendons were subsequently examined histologically and found to contain no ordinary ventricular muscle fibres, but fibres of primitive type only.

If a longer spurious tendon in a surviving dog's heart is connected with a string galvanometer by means of two non-polarisable electrodes it will invariably be found that the centrally situated contact becomes negative first. If the fibre is cut as near its central attachment as possible and an electrical stimulation is applied at the central end, a contraction wave can be seen to proceed peripherally and to cause a weak extra-systole in the appropriate ventricle wall. If the spurious tendon is tightly ligatured peripherally near the ventricle wall, this extra-systole does not appear unless the stimulus be very strong, in which case it is presumed that current has escaped to the ventricular muscle. Experiments very similar to the last, in which tendons have been stimulated, have been reported by Erlanger, and our findings are the same².

The contraction wave can also proceed centrally when the stimulus is peripheral.

Since the spurious tendons are similar in structure to the His bundle and its two divisions and consist chiefly of primitive muscle cells, these observations point to the conclusion that all these structures are involved by a contraction process during the passage of a normal stimulus from auricle to ventricle.

2nd series of experiments. If the His bundle is completely severed in the surviving dog's heart, automatic ventricular beating sets in, and the spurious tendons beat independently of the auricles and with the same rhythm as the ventricles. If the ventricle is brought to rest by reduction of the pressure of the perfusion liquid or by adding pilocarpine to the perfusion fluid, the rhythm of the spurious tendon fibres remains unchanged. By restoring the pressure of perfusion or by adding atropine to the perfusion fluid, respectively, the ventricle can be brought to beat again with the rhythm of the spurious tendons.

The following experiment serves as an example.

Dog weighing 11 kg. The temperature of the Locke's solution and in the apparatus was 38.5°C., and the pressure of perfusion 90 mm. Hg. The left ventricle was opened, and the ventricle and spurious tendons found to be beating at 85 per minute. The bundle of His was then severed; as a result a rapid irregular rhythm developed and lasted for 1 minute; the heart then beat regularly, both the ventricle and the spurious tendons having a rate of 78 per minute.

1.5 cc. of 10 per cent. pilocarpine in Locke solution was now introduced into the perfusion directly into the cannula.

5 minutes later the ventricle stood still while the spurious tendons continued to beat regularly at 78 per minute.

After another 15 minutes 2.0 cc. of 10 per cent. atropine in Locke's solution was injected. 10 minutes later the ventricle began to beat, at first irregularly and then regularly. Ventricle as well as spurious tendons beat in the same rhythm at 78 per minute.

A few of the spurious tendons were subsequently examined histologically and were found to contain only primitive muscle cells.

The same result can be obtained after section of both branches of the His bundle. From these experiments the conclusion may be drawn that the branches of the His bundle³ with their peripheral ramifications are capable of originating impulses.

3rd series of experiments. This automatic property can be shown, moreover, in isolated spurious tendons. If such tendons are placed in oxygenated Locke's solution and kept at body temperature, they can be seen to beat rhythmically for periods up to 10 hours. At room temperature, however, the duration of such automatic movement is seldom more than 10 or 20 minutes. Usually the beating is to be seen as soon as the tendon

is placed under the microscope, though the beats at first may be feeble: they become stronger. In other cases the beats are strong from the beginning.

The following experiment serves as an example.

Dog, of 12 kg. A spurious tendon of length 1.2 cm. was taken from the left ventricle and placed in oxygen-saturated Locke's solution at 38.5 C. and the rhythm of the spontaneous beats counted under the microscope over a period of 30 minutes.

Time.		Frequency per minute.
Hrs.	Mins.	
0	30	83 regular
1	0	83 ..
1	30	83 ..
2	0	79 ..
2	30	76 ..
3	0	76 ..
		76 ..
		76 ..
6	30	76 ..
		Locke's solution renewed.
7	0	80 ..
7	30	82 ..
8	0	82 ..
		Observation continued respnd.
10	30	92 somewhat irregular
11	0	92

Examined subsequently histologically, the spurious tendon was found to contain primitive muscle cells only.

4th series of experiments. If a spurious tendon is removed together with a small piece of the ventricular wall and stimulated with a single induction shock, the piece can be seen to contract under the microscope. This is the more evident, the less there is of true heart muscle present. Curiously enough the movement is most conspicuous at the thin transparent edge of the piece where the heart muscle is absent.

If a thin piece of the inner surface of the ventricle be removed and placed in warm oxygenated Locke's solution, it can be seen under the microscope to contract rhythmically, which contraction is the more conspicuous the less there is of actual heart muscle present. Presumably, in this experiment, the attached ventricular muscle does not respond to the rhythmic beating, but increases the resistance to contraction of the tissue which is active. The amount of muscle present was demonstrated histologically in each case. Small pieces of heart muscle used as controls either do not contract at all or do so only feebly, ceasing to beat after a few minutes.

Thus the Purkinje cells which lie directly under the endocardium and not those of the heart muscle itself appear in this class of experiment to be

responsible for the rhythmic contractions. An old assertion of Kölliker's² on the contractility of the endocardium is probably to be interpreted in this sense.

From the four series of experiments dealt with above it is possible to conclude that in the transmission of stimuli the whole system, including its terminal ramifications, contracts, and that in a normal heart beat a wave of contraction passes from the auricle to the ventricle by way of the primitive muscle cells of this system. It is thus unnecessary to assume a nervous mechanism for auriculo-ventricular conduction. Similarly it is correct to assume that this system has automatic properties. The histological examination of all the spurious tendons (dog and rabbit) used in the experiments reveals the fact that these consist specifically of primitive muscle cells, as in the His bundle and its branches, and that while they contain nerve fibres neither nerve cells nor nerve trunks are present. The presence of true heart muscle cells is very rare in these false tendons. It is clear, therefore, that the tissue elements of the system which possess automatic properties are the primitive muscle cells.

An interesting discovery made by Dr. Seizo Katsunuma⁴ may be here referred to, namely, that the muscle cells not only of the sinus node but also the primitive muscle cells of the entire system of the auriculo-ventricular bundle (from the A-V node to the terminal ramifications) are incomparably richer in indophenol oxydase than the actual cardiac muscle cells, a fact which is in perfect harmony with the above-mentioned vigorous activity of the former.

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THE INFLUENCE OF VAGAL STIMULATION UPON THE FORCE OF CONTRACTION, AND THE REFRACTORY PERIOD OF VENTRICULAR MUSCLE IN THE DOG'S HEART.*

By ALAN N. DRURY.†

(*Cardiac Department University College Hospital Medical School, London.*)

MANY observers have studied the influence of vagal stimulation upon the contraction force of ventricular muscle in the mammalian heart by myocardiographic methods. McWilliam⁶ considered that it exercised a definite control on the contraction force. Roy and Adami⁷ and Bayliss and Starling¹ came to the conclusion that vagal stimulation had no depressant action on ventricular muscle; while Knoll,³ Henderson and Barringer,² found that under moderate vagal stimulation which slowed the cardiac rate but little, the contraction force was augmented: a result explained not on any alteration of contraction force, but on the change of rate.

On account of the various types of myocardiographs used, and the diversity of the results obtained, it seemed desirable to test a myocardiograph of the Cushny type as an index of the force of muscular contraction and to decide the conditions which must be fulfilled in order that successive myograms may be compared without fear of error. One of the conditions necessary, as many workers have pointed out, is that the heart rate should remain unchanged; for a retarded rate by allowing a more complete recovery of the muscle will give rise to a stronger contraction, unless this slowing be so great as to allow an over-filling of the heart with consequent over-distension of the ventricular muscle, when the contraction is weakened.‡ There are, however, other factors which must enter into consideration.

It is well known that vagal stimulation, besides slowing the rate of beating of the whole heart, from time to time modifies the course of an

* The dogs used in these experiments were fully anaesthetised with morphia, followed by paraldehyde or chloretone with, if necessary, a sufficiency of ether.

† Working on behalf of the Medical Research Council.

‡ Curves which were interpreted by McWilliam as indicative of a weaker force of contraction have been criticised by Roy and Adami from this point of view.

excitation wave transmitted from the auricle to ventricle, thereby producing one or more abnormal ventricular contractions: while if its action is more intense, the excitation wave is blocked, and the ventricle responds to inherent stimuli, let loose in different regions. In either case the sequence of fibre contraction in the ventricle is modified.

A Cushny myocardiograph, like many others, records the variation in the length of a strip of muscle interposed between two fixed points, but the record is influenced by the direction of the muscle fibres relative to the points of the instrument's attachment. Fibres which run across, as opposed to those which run in the length of the instrument, will not produce shortening in the strip but will tend to lengthen it.* Change in the strip's length is a resultant of contractions in fibres running in several or many directions and is influenced also by contraction of the surrounding ventricular muscle; the excursion obtained depends therefore upon several factors and not least, as will be shown, upon the sequence in which the various muscle elements contract.

The influence of sequence of fibre contraction upon the myogram can be shown best by rhythmic stimulation of the heart at a fixed rate from various regions of the ventricular muscle. This has been done in a number of animals, the rhythmic break shocks being thrown into the muscle at various points by means of fish hook electrodes at a rate slightly exceeding that of the normal heart beat. The stimulating circuit from the secondary coil was divided into two limbs and a switch over key inserted, so that by connecting the two limbs to two stimulating electrodes the stimulus could be passed into either electrode at will. One limb of the stimulating circuit was connected with a fish hook electrode throughout the experiment, and the other limb connected to the various points in turn, and the resultant myograms compared with the standard myogram.

The myocardiograph was sewn, in the usual manner, into the epicardium of the right ventricular muscle, about midway between base and apex and at right angles to the axis of the heart, a position being chosen which gave a good shortening of the muscle between the swinging arms. The record of shortening was obtained in the earlier experiments by transmitting the movements of the swinging arms of a Cushny myocardiograph to a light spring lever fixed in front of the camera by means of a fine thread. In later experiments an optical recorder was used. A small myocardiograph was

* On examining unpublished records taken in this laboratory by means of the polymyograph¹, of normal ventricular contraction, in which movements of a line of points on the ventricular surface, relative to each other, are recorded, it is seen on occasions that while certain adjacent points are definitely approximated, others are not. Although contraction is occurring over the whole muscle strip on which the points lie, some points adjacent to each other retain their relative position in systole, while others actually move apart, especially is this the case if no artificial tension is placed on the muscle. No myograms were obtained in this series which showed slight or reversed movement, but the position and tension of the myocardiograph was specially chosen to obtain myograms of good amplitude. If the position and tension be less carefully chosen, myograms of slight amplitude or reversed movement would be expected on occasions.

used,* between the swinging arms of which a small tambour was interposed, the movements of this tambour being transmitted by air to a Franks capsule. The arterial pressure was recorded by a Hürthle manometer connected with the left carotid artery. A simultaneous electrocardiogram was obtained by lead *II*.

A series of such records was obtained from six dogs. The records showed that the myograms from a constant part of the ventricular wall presented material changes in both form and amplitude on changing the point stimulated. The shape of the curve maintained in general its usual plateau form, but variations in the rate at which the upstroke or the downstroke was written, and the presence of deep notches in one or other limb, gave rise to many different forms. The amplitude of the curve varied considerably, and records were often obtained in which, upon changing the position of rhythmic stimulation, it was reduced by one third or more. The original form and amplitude always returned when the stimuli were transferred again to the original point.

In Figs. 1, 2 and 3, the amplitude of the myogram is seen to decrease upon changing the position of the stimulating current, while a comparison of the beginning of Figs. 1 and 2 (records which were taken within a moment of one another) shows the return of the myogram to its original form when the first point of stimulation is again used. Myograms of changed form and amplitude are therefore readily obtained when the position of stimulation is changed. Under these circumstances, the changed amplitude does not indicate an altered force of contraction, for the rate of beating has been maintained constant throughout, and the condition of the ventricular muscle has remained unchanged. It is to be ascribed to the altered sequence of fibre contraction. The arterial curve shows only minor variations throughout the records. In Fig. 1, for instance, the arterial curve is immediately lowered a little when the electrodes are changed, indicating a lowered arterial pressure, the myogram being smaller at the same time. On the other hand, in Fig. 2 the arterial curve is seen to rise slightly after the change: it occurs, not on the first beat,† but at the second beat following movement of the reversing key: this arterial rise is also associated with a smaller myogram. The same conditions are found less conspicuously in Fig. 3. Such arterial changes are often seen, but no constant relationship exists between the change in amplitude of the myogram and of the arterial record. They add further evidence that the amplitude of the myogram is not a true index of the force of ventricular contraction. They are expressions of altered sequence of contraction which gives rise to less or more efficient heart beats.

The electrocardiograph records the usual forms of curve associated with ventricular extra-systoles liberated from the various points stimulated.

* Similar in design to that described by Wiggers.*

† The first beat is liberated in the body of the left ventricle, and follows on a beat which has spread from the right ventricle; it is, therefore, relatively premature in the left ventricle, and consequently gives rise to a smaller arterial curve.

The influence of vagal stimulation upon the force of contraction. It is now evident that ventricular myograms are only comparable provided that the rate of beating is maintained constant and that the sequence of the ventricular contraction is unchanged: if these conditions are fulfilled by stimulating at a fixed point over periods during which the vagi are stimulated, the influence of such stimulation upon the force of contraction can be investigated without fear of error.

In such circumstances the electrocardiograms remain constant in form, and conduction from point to point remains unaltered over the period during which the vagi are stimulated, as the following observations show. Such differences as appear in the transmission intervals are no more than may be accounted for by error in measurement.

TABLE I.

Influence of vagal stimulation upon rate of conduction in left ventricular muscle.

Dog.	Rate.	Electrode distance.	Transmission times in secs.		
			Normal.	Right vagus.	Left vagus.
P.R.	175	13 mm.	0.034	0.033	0.037
	175	13 mm.	0.033		0.035
P.S.	210	6 mm.	0.013	0.013	0.013
	210	6 mm.	0.013	0.012	0.013
P.T.	260	6 mm.	0.012	0.012	0.012
P.U.	210	8 mm.	0.035	0.038	0.036

Many myograms were obtained, some recorded with the spring lever, others optically, of the ventricular contractions, beating at a constant rate of usually about 160-200 per minute both before and during vagal stimulation, in six dogs. The vagi were tested separately in each instance.

Fig. 4 (*Dog Q.X.*, record 14) is an example of such a record, the ventricle being rhythmically driven at a point to the right of the arms of the myocardiograph, which was fixed at right angles to the axis of the heart, in the body of the right ventricle. The myogram has been optically recorded, and maintains its form and height absolutely unchanged throughout the record. For the first four beats, the *R* wave of the electrocardiographic record is followed by an abnormal auricular complex *P*: on the fourth beat the right vagus is strongly stimulated (sufficient to completely arrest the normally beating heart a moment later), and complete block is produced between ventricle and auricle and the auricular complex is lost. The arterial curve shows a slight and progressive rise throughout the period of vagal

stimulation.* Similar negative results in the myogram were seen on stimulating the left vagus nerve. No records have been obtained which showed any variation in the myogram during vagal stimulation: from this it can be concluded that such stimulation has no effect upon the force of ventricular contraction.

The influence of vagal stimulation upon the refractory period.

The refractory period of ventricular muscle was tested in a large series of dogs, both before and during stimulation of both vagi separately. The ventricle was driven by means of rhythmic break shocks sent in through fish-hook electrodes embedded in the muscle of the right or left ventricle, and the refractory period tested, in a manner previously described in detail⁵. In the following table the values are tabulated for a series of 15 dogs, the ventricular rate of beating varying from 136-218 per minute in the different dogs. Table II, in which the readings are tabulated, show that, in contradistinction to its effects upon the auricle, vagal stimulation does not shorten the ventricular refractory period: on the other hand, there is a tendency for the period to become prolonged under vagal stimulation. This does not occur in all the experiments, and when present amounts rarely to more than 0.02 of a second. As this rise is a small one, and does not invariably occur, it is not, perhaps, to be emphasised, but the table clearly shows that under vagal stimulation the refractory period does not shorten. Possibly such slight lengthening as occurs is produced by the slight rise of arterial pressures described as accompanying the reaction.

Comment.

It has been shown that the ventricular myocardiogram cannot be used to compare the strength of fibre contraction from beat to beat, unless two factors are known to be constant. The first is the rate at which the ventricle is beating, and the second is the sequence of fibre contraction. In previously published observations, dealing with the influence of vagal stimulation upon the force of ventricular contraction, the naturally beating heart has been used, and the heart rate has slowed during the period of vagal stimulation: the influence which slowing may exert upon the resultant curves has been recognised by previous workers, who have attempted to make allowances for it. It is questionable if such allowances can be fairly made. The second factor, namely, possible change of sequence of fibre contraction has been neglected. That such change of sequence frequently occurs under vagal stimulation is well known: that it materially affects the resultant curves is now shown. It is suggested that in instances from past records

* This rise is seen in practically all the curves during vagal stimulation. It does not pass away till 10-15 beats have elapsed after vagal stimulation is withdrawn. Its meaning is at present unknown, but it is presumably non-cardiac in origin.

TABLE II.

*The influence of vagal stimulation upon the refractory period of ventricle.**

Dog ...	P.P., R. ventricle.			P.Q., L. ventricle.			P.R., L. ventricle.		
Rate ...	136	135	136	210	210	210	174	172	174
	Normal.†	R. vagus.	L. vagus.	Normal.†	R. vagus.	L. vagus.	Normal.†	R. vagus.	L. vagus.
			0.238						0.226
0.213		0.270	0.237	0.178	0.201		0.200	0.234	0.218
0.192		0.266	0.233	0.174	0.190	0.226	0.185	0.222	0.214
0.189		0.249	0.216	0.171	0.185	0.204	0.176	0.209	0.212
0.182		0.229	0.212	0.165	0.179	0.198	0.172	0.206	0.208
0.177		0.225	0.208	0.164	0.176	0.198	0.167	0.202	0.186
0.175		0.216	0.204	0.161	0.173	0.192	0.163	0.179m	0.174
0.164	0.156	0.181		0.160	0.172	0.167	0.156	0.178	0.171
0.132	0.149	0.181		0.156	0.184	0.158	0.150	0.174	0.157
0.137	0.160	0.167		0.140	0.151	0.134	0.145	0.172	0.145
0.135	0.169	0.152		0.139	0.159	0.129	0.142	0.166	0.143
0.130		0.146		0.132	0.151	0.121	0.135	0.154	0.140
									0.139

Dog ...	P.S., L. ventricle.			P.T., L. ventricle.			P.U., L. ventricle.	
Rate ...	210	210	210	210	210	210	210	210
	Normal.†	R. vagus.	L. vagus.	Normal.†	R. vagus.	L. vagus.	Normal.†	L. vagus.
						0.169		
						0.163		
0.200		0.198	0.202		0.168	0.165	0.152	
0.188		0.184	0.197	0.176	0.163	0.161	0.142	0.163
0.187		0.177	0.194	0.167	0.160	0.153	0.139	0.154
0.185		0.172	0.188	0.162	0.160	0.143	0.132	0.149
0.178		0.165	0.183	0.159	0.156	0.141	0.128	0.140
0.172		0.160	0.178	0.144	0.154	0.138m	0.123	0.138
0.153	0.150	0.174		0.141	0.136		0.116	0.130
0.151	0.146	0.171		0.130	0.138	0.135	0.104	0.117
0.142	0.142	0.148		0.129	0.125	0.135	0.100	0.116
0.139	0.139	0.144		0.122	0.132	0.124	0.092	0.111
0.137	0.130	0.140		0.118	0.130	0.113	0.080	0.098
		0.127						

* Figures higher than those tabulated invariably gave responses, while those lower invariably failed. Break shocks have alone been tabulated, except in certain experiments when the make shocks are included, they are marked *m*. The strength of the testing shock was about 10 times above threshold value.

† Vagi cut.

TABLE II.—*continued*.

<i>Dog</i> ...	<i>P.V.</i> , L. ventricle.			<i>P.Y.</i> , L. ventricle.			<i>Q.D.</i> , L. ventricle.		
<i>Rate</i> ...	210	210	210	215	215	215	212	212	212
	Normal.†	R. vagus.*	L. vagus.*	Normal.†	R. vagus.*	L. vagus.*	Normal.†	R. vagus.*	L. vagus.*
									0.163
									0.158
	0.142	0.151	0.162	0.140			0.168	0.177	0.154
	0.136	0.145	0.159	0.138	0.149		0.164	0.164	0.152
	0.129	0.142	0.158	0.129	0.134	0.137	0.155	0.162	0.146
	0.126	0.139	0.143	0.123	0.130	0.123	0.152	0.162	0.146
	0.123	0.137	0.142	0.120	0.125	0.119	0.148	0.159	0.143
	0.119	0.126	0.136	0.115	0.118	0.115	0.139	0.150	0.137
	0.112	0.125	0.124	0.096	0.117	0.112	0.125	0.144	0.134
	0.111	0.117	0.121	0.095	0.107	0.108	0.124	0.142	0.131
	0.098	0.110	0.119	0.094	0.106	0.107	0.120	0.137	0.124
	0.092	0.101	0.102	0.089			0.118	0.128	
	0.091								
<i>Dog</i> ...	<i>Q.E.</i> , L. ventricle.			<i>Q.F.</i> , L. ventricle.			<i>Q.G.</i> , L. ventricle.		
<i>Rate</i> ...	200	200	200	171	171		218	218	218
	Normal.†	R. vagus.*	L. vagus.*	Normal.†	R. vagus.*	L. vagus.*	Normal.†	R. vagus.*	L. vagus.*
					0.200				
	0.169	0.211	0.195	0.196	0.196	0.211		0.157	
	0.168	0.194	0.182	0.183	0.194	0.200	0.148	0.155	0.152
	0.162	0.187	0.180	0.180	0.199	0.197	0.140	0.153	0.145
	0.155	0.172	0.177	0.175	0.182	0.196	0.137	0.149m	0.141
	0.152	0.169	0.166	0.173	0.184	0.195	0.132	0.137m	0.139m
	0.151	0.165	0.160	0.171	0.183	0.184	0.129	0.134	0.139
	0.148	0.163	0.154	0.166	0.161	0.181	0.127	0.130	0.137
	0.137	0.137	0.143	0.165	0.142	0.179	0.119	0.130	0.135
	0.133	0.126	0.143	0.157	0.140	0.173	0.113	0.121	0.131
	0.120	0.124	0.140	0.146		0.173	0.100	0.119	0.123
							0.089		
<i>Dog</i> ...	<i>Q.J.</i> , L. ventricle.		<i>Q.Q.</i> , L. ventricle.		<i>Q.R.</i> , L. ventricle.				
<i>Rate</i> ...	200	200	214	214	214	214			
	Normal.†	L. vagus.*	Normal.†	L. vagus.*	Normal.†	L. vagus.*			
	0.150	0.162	0.180	0.178	0.168	0.168			
	0.142	0.160	0.168	0.175	0.159	0.151			
	0.139	0.155	0.161	0.170	0.151	0.147			
	0.124	0.144	0.156	0.161	0.140	0.140			
	0.124m	0.143	0.154	0.160	0.135	0.136			
	0.124	0.137	0.153	0.159	0.132	0.127			
	0.120	0.129	0.152	0.150	0.127	0.129			
	0.118	0.123	0.151	0.145	0.127	0.127			
	0.116	0.122	0.147	0.144	0.125	0.123			
	0.103	0.110	0.136	0.140	0.125	0.110			
						0.109			

* Ventricle not brought to standstill upon vagal stimulation.

where decreased amplitude of the myogram under vagal stimulation is apparently not to be explained on the ground of altered heart rate, altered sequence of fibre contraction has been responsible. When both rate and sequence of fibre contraction are maintained constant, change in the force of the ventricular contraction, as evidenced by the myocardiographic curve, under vagal stimulation is not seen. It is concluded, therefore, that the vagus has no effect on the contraction force of the ventricle: and this conclusion is supported by the further observation that vagal stimulation has no shortening effect on the refractory period of the ventricular muscle.

Conclusion.

Vagal stimulation (right and left) in the dog has no influence on the force of the ventricular contraction. It does not shorten the refractory period of the muscle as it does in the case of the auricle.

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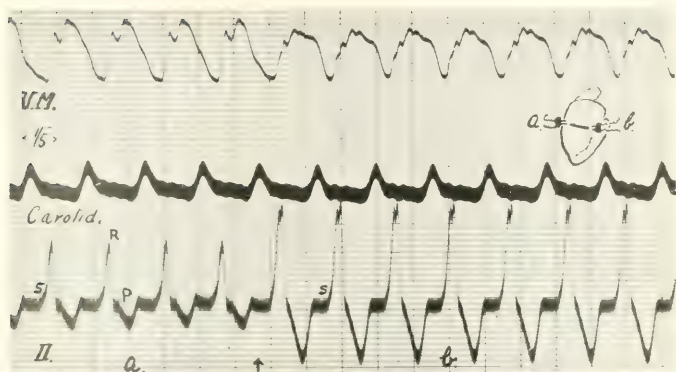


FIG. 1.

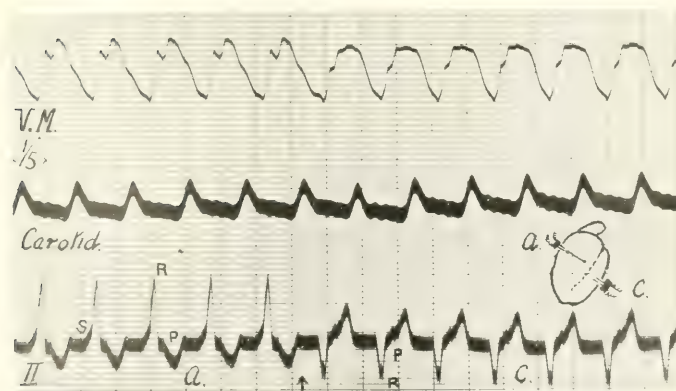


FIG. 2.

FIG. 1. *Lead II*, *Q.N.* record 149. FIG. 2. *Lead II*, *Q.N.* record 22. Myograms of the carotid artery (also rectified with rhythmic beats indicated) from different points of the ventricle. The position of the manometer is shown in the sketch as a black line, and the position of the stimulating electrodes is indicated. The position at which the stimulus current was triggered is shown by an arrow. *V.M.*, ventricular myogram. *Carotid.*, Record obtained with a Hürthle's manometer. *II*, Lead *II*, electrocardiographic record. *S*, stimulus stimuli. *b.*, Ventricular complex. *P*, auricular complex.

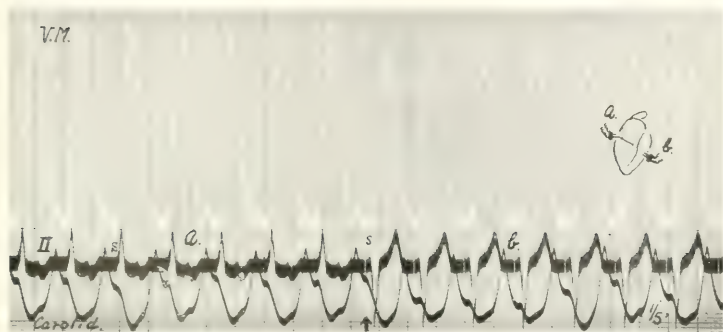


FIG. 3. Dog R.A. (crossed 14). (14). Myograms of the right ventricle associated with rhythmic beats liberated from different points of the ventricle. The position of the myocardiograph is shown in the sketch as a black line, and the position of the stimulating electrodes is indicated. The position at which the stimulating current was changed is shown by an arrow. V.M.—ventricular myogram. Cardi. G.—Record obtained with a Hürthle's manometer. II—Lead II, electrocardiographic record. S—rhythmic stimuli. R—ventricular complex. P—ventricular complex.

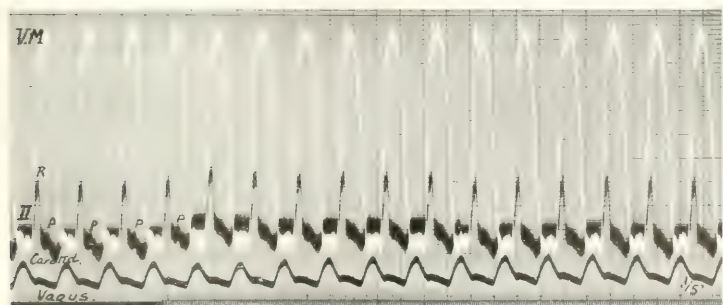


FIG. 4. Dog R.X. (crossed 15). (15). Influence of vagal stimulation upon the myograms of the right ventricle. The myocardiograph lay at right angles to the axis of the heart, mid-way between base and apex of the right ventricle. The stimulating electrodes were fixed in the body of the ventricle to the right of the myocardiograph. Description of lettering as in previous figure.

HEART.

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Wm Baylis

SIR WILLIAM MADDOCK BAYLISS, M.A., LL.D., D.Sc., F.R.S.

Professor of General Physiology, University College, London.

THE death on August 27th, 1924, at the age of 64, of William Maddock Bayliss closed a career of single-minded devotion to physiology as a subject of pure research, and of world-wide influence on its development as an exact science. During his later years his predominant interest was the physico-chemical basis of vital phenomena, but he made, by himself and in collaboration with others, many contributions of the greatest importance to the physiology of the circulation.

Born in 1860, as the only son of a Wolverhampton iron manufacturer, Bayliss was happily free to follow the natural bent of his genius. A business career proving unattractive, he became a student of medicine, and, after a period of old-fashioned apprenticeship, entered University College, London, in 1881. He was destined to remain associated with that foundation, and with its School of Physiology, for the whole of his scientific career. He soon fell under the spell of Burdon Sanderson, and his interest, though its range was unusually wide and grew with the years, became centred on physiology. While still in the early stages of a medical curriculum, which he never completed, he is found co-operating with J. Rose Bradford in an investigation of the electromotive phenomena accompanying secretion. Burdon Sanderson had by this time left London for the chair of physiology at Oxford, being succeeded by Schafer. In 1885 Bayliss entered Oxford as a student at Wadham College. After three years, having taken an honours degree in physiology, he returned to University College, London, and remained there, actively engaged in physiological research, until his final illness.

With the return to London Bayliss entered upon a series of researches concerned with the physiology of the circulation. In 1893 he published his first paper on the action of the depressor nerve, showing the general distribution of the reflex vaso-dilator effect, which, at that time, he was

inclined to attribute to inhibition of the vaso-motor centre. This conception he later revised, when he demonstrated the vaso-dilatation produced by stimulation of the dorsal nerve-roots, long previously recorded by Stricker, but never generally accepted, until the two masterly papers by Bayliss put its reality beyond dispute. On the significance of this effect for the regulation of the circulation, and its bearing on the nature of the vaso-motor centres, he continued to work and to publish intermittently until 1908. Meanwhile, in collaboration with other workers, he had been exploring the circulatory mechanism in other directions. Papers were published during 1894-1895, with Bradford on the innervation of the limb vessels, and with Leonard Hill on the cerebral circulation.

In 1890 he began his collaboration and friendship with E. H. Starling, maintained to the end, and rendered closer on the personal side by his marriage, in 1893, with Starling's sister. The first three papers which they published jointly dealt with the physiology of the mammalian heart. The first dealt with the form of the electrical variation in the mammalian ventricle, giving, with the apparatus then available, a picture which all subsequent work has confirmed, though knowledge of the conducting mechanism was then inadequate for its interpretation. It is worthy of note that the authors indicated its incompatibility with a mere muscular conduction in the wall of the ventricle. The second paper dealt with some points in the innervation of the mammalian heart, and the third with records of the intraventricular pressure in mammals, using a method thoroughly characteristic of Bayliss's instinct for simplicity combined with precision. In the same year (1894) appeared the important paper on venous and capillary pressure, laying firmly the physical foundation on which Starling built his conceptions of the formation of lymph and urine. Between 1899 and 1901 the collaborators published their work on the movements and innervation of the intestines, and in 1902 described what is, probably, the most widely known of their joint discoveries, that of secretin, and the humoral control of pancreatic secretion, thereby giving a great new impetus to the study of the chemical mechanisms of co-ordination in the body.

The work on secretin gave a new opportunity for examining the mode of action of the pancreatic enzymes, and Bayliss was soon deep in a series of fundamental enquiries into the nature of enzyme action in general, on which

he produced, in 1908, an invaluable monograph, now in its fourth edition. During the decade before the War we find him, with occasional recurrence to his earlier love of the vaso-dilator mechanisms, chiefly occupied with the physico-chemical properties of heterogeneous systems, always with a view to their bearing on the ultimate nature of vital phenomena.

It was the publication, in 1914, of his great book, the "Principles of General Physiology," which first revealed, to those beyond an intimate circle of his colleagues and pupils, the extraordinary range and depth of his knowledge, and the orderly treasure-house of his mind. Only Bayliss was surprised at the enthusiasm with which it was received. He had written simply and without artifice, as he was wont to talk in private, of the things which had interested him, and of his thoughts about them, without any idea that the plain record would show him to the world as a master. Workers in all departments of Science awoke to a full appreciation of his quality. In 1919 the Royal Society gave him its highest honour, in the award of the Copley Medal.

During the War Bayliss eagerly applied his great experience of the factors controlling the circulation, and of the osmotic properties of colloids, to devising methods of replenishing the circulatory volume, depleted by hæmorrhage or shock. In the later years honours fell thick upon him, who had avoided rather than sought them. The knighthood, which came to him in 1922, gave unmixed pleasure to all who knew him.

To British physiologists the personal loss is inseparable from that to their science. There was none other of their circle in whose life the Physiological Society formed such a central interest. He bore for years the burdens of its offices with his invariable equanimity, and, till his last illness, was always to be found at its meetings. Even here, among his friends, he was reluctant and unready in open debate, and anxious rather to efface than to obtrude himself; but his quiet personality pervaded the Society, and had a large share in maintaining its atmosphere of genial comradeship and friendly informality.

Troubled neither by personal ambition nor by material anxiety; with unfettered opportunity to do the work which he loved, in his laboratory

at University College or in that which he made in his beautiful Hampstead garden ; with an extraordinary equability, both of temperament and, until his last and only real illness, of physical health ; Bayliss seemed to have all that could make for happiness in unusual perfection. There can be no doubt that he had it. In his home and with his family, in a circle of friends sharing his interests and of students seeking help and inspiration, he enjoyed and radiated a quiet happiness, and kept it to the end.

H. H. D.

AURICULAR FIBRILLATION IN THE DOMESTIC ANIMALS.

By J. ROOS.

(*From the Physiological Laboratory of the University of Leyden.*)

A great part of our insight into what auricular fibrillation really is, we owe to the fact that in the mammalian heart, especially in that of the dog, the auricles are susceptible to this condition. After the attention had been called to this by McWilliam⁷, various investigators, of whom we will mention L. Fredericq², Rothberger and Winterberg⁹, and Lewis³, have made use of this susceptibility to study fibrillation experimentally. The frequency with which domestic animals develop auricular fibrillation spontaneously is at present unknown.

Only a few cases in the horse, observed by Lewis, have been recorded. After having examined a great number of animals of the English army and of veterinary clinics for irregularity of the heart beat, he found this disturbance in six horses only. Lewis considered it a rare disease. Records of the conditions in other domestic animals are non-existent.

The following are instances of fibrillation of the auricles which have come under my own observation.

Case 1. A twelve-year old mare in foal showed a pulsus irregularis perpetuus: the number of ventricular beats amounted in the average to 72 per minute (normally 40). The heart sounds were pure: the heart was not enlarged. Respiration was accelerated to 22 (normally 12) and the expiration strengthened by abdominal contraction. The veins were not overfilled, and there was no dropsy. After slight exercise pulsation occurred in the lower third of the jugular veins.

During the further progress of the disease the rate of ventricle gradually diminished, and after eight months it had fallen to 45. This decrease in frequency was attended, however, by decreased efficiency. Whereas in the beginning the animal could still be used for light work, during the last month, after the rate had diminished to 50, it could work no more. After a few minutes of exercise dyspnoea occurred and no further work was possible. Previously exercise had accelerated the pulse from 60 or 70 beats to 100, now increase in rate was either insignificant or absent. Dropsy did not

supervene: even the hypostatic cedema of the legs, which horses having no special circulatory affection often show, when kept in stable for some days, did not appear.

The normal electrocardiogram of a horse is published in Fig. 1: it was first recorded in this laboratory 15 years ago, and it has been published by different authors, *e.g.*, by Tschermak¹⁰ and Marek⁸.

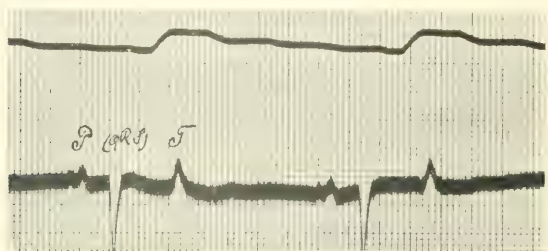


Fig. 1. Normal electrocardiogram of a horse, lead from fore-chest and left lower chest. Accompanied by an arterial record from the art. maxillaris externa. *P* auricular summit, *QRS* and *T*, ventricular complex. Ordinates = 10^{-4} volts; abscissæ = 0.04 of a second, in this and subsequent figures.

Fig. 2 is an electrocardiogram from the first case. The curve has been taken by connecting the right part of the fore-chest near the scapulo-humoral joint and the left part of the lower chest near the apex beat. Besides a great irregularity of the ventricular complexes it shows the characteristic oscillations of a fibrillating auricle. There is no *P* summit, and in its stead we find the oscillations *f*. Contrary to the instance published by Lewis, this curve does not show these oscillations locally, but they are clearly visible along the whole curve. Their frequency is about 450 per minute, which rate corresponds to the rate found for man.

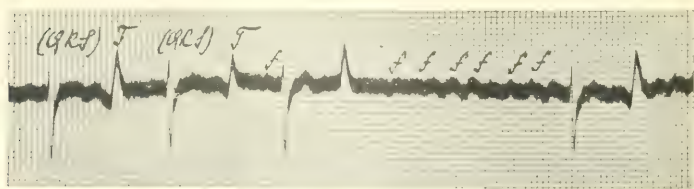


Fig. 2. Auricular fibrillation in Case 1. Lead from right fore-chest and left lower chest. The *P* summit is lacking; in its stead are the very frequent irregular oscillations, *f*.

As a rule animals from whom electrocardiograms are to be taken are of a sufficiently quiet behaviour when in quiet surroundings. The skin is well moistened with a 20 per cent. hot solution of sodium chloride, before applying the electrodes, to well damp the hair. If the limbs are connected to the galvanometer, the bandages described by Einthoven¹ are particularly suitable. They may be easily fastened to metacarpus and metatarsus and give only a slight skin resistance, while movements of the animal cause little or no alteration of the resistance nor polarisation. To connect the trunk, as in Fig. 2, square amalgamated zinc plates may be used having a surface of about 100 square centimetres. They are covered on one side with moist cotton wool and next wrapped in absorbent gauze, also soaked beforehand in a 20 per cent. solution of sodium chloride and connected to the galvanometer.

After the animal described had shown auricular fibrillation for eight months, the condition became worse in spite of treatment, and it was killed. The heart was examined in the Pathological Institute of the Veterinary University at Utrecht by Professor Schornagel, to whom I am indebted for the following notes. The greatest alteration was shown by the auricles; here a strong formation of connective tissue occurred. In some parts of the microscopical preparation it occupied more than half the field. Fresh inflammatory foci were lacking, though the connective tissue was still new and showed an active appearance. The muscle fibrils showed degenerative changes: they were pale, somewhat swollen and showed vacuolation. Transverse striation was indistinct; longitudinal striation, however, was clearer than in normal cases. In the wall of the right auricle an artery containing an organised thrombus was found. The fibres of the bundle of His and the Purkinje cells were coloured irregularly and were often granular.

Case 2. A middle-aged cart horse (gelding, seven years old) having been in a meadow during the night, was found to be listless and sluggish in the morning and could not be used for its work. It could hardly be made to walk and refused to trot. I found this animal, previously spirited, with half closed eyes and drooping head, languid before its manger. It did not respond to anything and refused its food. The respirations were accelerated to 20, and abdominal movements were vigorous. The pulse rate was diminished to 20. The pulse rhythm was irregular and the irregularity was of a very disorderly kind. Two succeeding beats were rarely of the same strength and the pauses changed in duration continually. The heart sounds were free from murmurs. Slight exertion caused considerable dyspnoea, the pulse rate remaining constant. Venous pulsation was not to be seen. The body temperature was normal. For a month there was general improvement and a regular pulse of 48 beats per minute became established. Then the pulsus irregularis perpetuus returned, and to the earlier symptoms attacks of unconsciousness were added. These occurred both during the day and

night and were often repeated. Now the arteria maxillaris externa showed a pulse rate of 16, the heart beating at 25 per minute. The heart sounds varied in intensity and duration. The first was lengthened, very unequal and of a rumbling quality; the second was sometimes attended with a buzzing noise which could not be exactly defined. The jugular veins now showed distinct pulsation. Atropine in a dose of 100 milligrammes accelerated the pulse rate to 26. The pulse pauses were strikingly unequal, varying between 2 and 20 seconds. As soon as a pause of 18 seconds had elapsed, the horse began to lose balance and threatened to fall. A fall, however, never happened in my presence, a pulse occurring and the animal recovering itself. It is remarkable that with a pause of 20 seconds no further manifestations of cerebral anæmia appeared, but only the initial disturbance of body balance. In man, in whom the pulse rate is about twice as frequent as in the horse, a pause of 3 to 7 seconds often leads to loss of unconsciousness^{4, 5}.

A month after the first attack had occurred death took place. Dissection revealed an enlarged heart, weighing 4,650 grams (the normal weight for this horse may be taken as about 4,000 grams). The left ventricle wall was hypertrophied. The valves looked normal. Microscopic examination showed no alteration of the muscular tissues.

Case 3. An old mare of 16 years showed an absolutely irregular pulse. It was a mixture of beats of greatly differing size, and pauses of varying length. The somewhat increased pulse rate of 54 corresponded to the rate of heart beat. There were no murmurs. Cardiac hypertrophy was apparent because, in spite of chronic lung emphysema, the boundaries of the heart dulness had kept their normal places. The jugular veins showed a systolic pulse wave. After the animal had trotted a few yards the pulse rate increased to 120, irregularity persisting. The animal was used afterwards for upwards of six months for rather heavy work at a walking pace, without its owner observing anything wrong with it.

Case 4. A young trotting mare, kept in a loose box, was called one morning by name, and dropped sideways to the ground with extended neck. The animal remained motionless for a few seconds and then got up without showing any further disturbance.

On examination the pulse rate was 30 and showed no irregularities. On the mare being called, the rate increased suddenly to 60, and an irregularity of the pulse became manifest. After a few minutes this acceleration vanished as suddenly as it had come; on close observation a slight inequality of the pauses could be perceived. Slow walking caused a quickening of the pulse rate of 35 to 45, while quick walking soon brought the pulse to 120 beats per minute, and pulsation became visible in the jugular veins. The heart sounds remained pure. The breathing was but little accelerated, but abdominally strengthened.

It appears from the above cases that auricular fibrillation occurs in horses of different sex, various age, and various breed. From the fact that the four cases occurred within a year among the patients of a private practice it may be concluded that the condition is not so rare as has been supposed. As in the case of man, the continued irregular pulse is the most striking symptom. However, with slow heart action it sometimes needs a close observer to discover this irregularity, a fact which is also true in the case of man. Whereas, however, in man most cases of auricular fibrillation present an increased rate of heart beat, a relatively slow ventricular action seems more frequent in horses. In none of the animals observed at rest was there a material quickening of the pulse. In two the rate was decreased, in one even to less than half the normal rate. And in the animal that had initially shown an acceleration to 70, the rate diminished to the normal during the further course of the disease. This decrease of rate was attended by decreased efficiency of the heart and by an aggravation of the general condition. The low ventricular rates suggest an involvement of muscle other than that of the auricle and especially the conducting fibres. Partial heart block is not uncommon in horses. The degree of block governs the ventricular rate.

It should be mentioned that disease of the mitral valve occurred in none of the cases described, though it is frequent in corresponding human patients. One of the horses had shown clinically a systolic murmur: dissection, however, showed healthy valves. This is not so surprising since diseases of the endocardium is rare in horses.

As regards the treatment, it may be mentioned that the use of neither digitalis nor strophanthus appears to ameliorate the disease. Thus, in *Case 1* on two occasions, 30 grammes of powdered digitalis leaves were given over a period of 5 days: the pulse remained irregular and its rate unchanged. A course consisting of 240 grammes of strophanthus tincture was given in 10 days; and after an interval of two days was repeated with similarly negative results. Similar treatment with strophanthus in *Case 2* led to no lowering of heart rate. In this case quinidine sulphate was also given. The first course consisted of three doses of 10 grammes for 3 days, and 3 doses of 20 grammes on the 4th day. The pulse became regular and the general condition improved. But after a week, without treatment, irregular heart action returned. During the second course death occurred, the animal having taken three doses of 10 grammes for 2 days only.

Of spontaneous auricular fibrillation in dogs I am unable to find any records. Lewis⁶ tried to discover the disturbance in this animal but soon desisted. He gave up the hope of obtaining the material he required from this source; on account of its obvious rarity and the presence of the natural respiratory arrhythmia, he could neither collect cases himself nor rely upon the observations of others in identifying the irregularity sought.

The three cases I have observed all occurred in middle aged male animals, namely of 4, 6 and 9 years of age. The *pulsus irregularis perpetuus*

was clearly perceptible in all three, there being in each instance no fixed relation between pulse size and length of the preceding diastole. Contrary to the experiences with horses, in two cases the pulse rate was increased to twice the normal. In none of the cases were the lesions of the heart restricted to the auricles. Two of the animals showed a greatly enlarged cardiac muscle and signs of insufficiency manifested during the course of the disease by ascites which would speedily have caused death, had not the animals been killed. The third dog presented, besides auricular fibrillation, hypertrophy (known to be of at least a year's standing) and a presystolic mitral murmur, which vanished when fibrillation set in. Death occurred suddenly in this case. The electrocardiogram of one of these animals is shown in Fig. 3. The curves again show complete irregularity of the

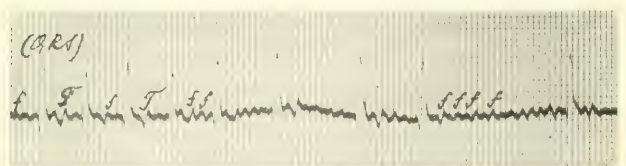


Fig. 3. Spontaneous auricular fibrillation in a dog. Lead from the right fore leg and the left hind-leg. There is no *P* summit; in its stead are very frequent irregular oscillations *f*. The ventricular complexes are irregular.

ventricular action. The cardiac intervals vary from 0.08 to about 1 second. The height of the *QRS* complex varies without relation to the duration of the preceding interval. This is particularly clear in the first four groups of alternate height in the figure. Along the whole curve oscillations *f* may be noticed, showing a frequency of 1,000-1,100 per minute, a figure which is slightly higher than that found in the dog with artificial auricular fibrillation.

SUMMARY.

1. Four cases of auricular fibrillation in the horse and three cases in the dog are described.

2. In the horse the affection is not a rare one. Comparing the clinical picture with the affection in man the following points may be noted: (*a*) The *pulsus irregularis perpetuus* is the most striking symptom. (*b*) As a rule the pulse rate is not increased. In one of the cases it was even decreased to less than half the normal rate. (*c*) There were no murmurs; post-mortem examination showed healthy valves.

3. In the dog the affection is a rare one indeed. (a) The pulsus irregularis perpetuus is the most striking symptom. (b) In two of the three cases the pulse rate was increased to twice the normal. (c) In one of the cases there was a presystolic mitral murmur which vanished when fibrillation set in.

4. In the electrocardiogram the oscillations of fibrillation are clearly visible along the whole curve. Their frequency is about 450 in the horse and 1,000-1,100 in the dog.

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THE AORTIC LESIONS OF SUBACUTE INFECTIVE ENDOCARDITIS.

By RONALD T. GRANT.*

(*Cardiac Department, University College Hospital Medical School.*)

THE following report is based on the examination of 30 cases of subacute infective, or bacterial, endocarditis. Of this series 26 have been previously reported from other points of view† and to these, 4 new cases are now added. The origin of the aorta, including the sinuses of Valsalva, is not infrequently involved by the disease process in this type of endocarditis, and the lesions may be conspicuous, as for example, the vegetations and aneurisms which are well known to occur in these situations. In some cases, however, they may only be discovered by close attention to macroscopic detail, and occasionally their presence is not revealed until a histological examination has been undertaken.

A survey of past records shows that when inflammatory lesions of the aorta are associated with a valvular endocarditis and when adequate clinical and pathological data are given, the endocarditis is usually, though not always, found to be of the subacute infective type. Such lesions have for a long time been a subject of considerable interest and controversy, particularly with regard to their origin and development, whether the primary event has been an infection from the lumen of the aorta, or whether they have originated in an embolism of a nutrient vessel arising from the coronary arteries. Eppinger's³ work on mycotic aneurisms forms the basis of most of our present knowledge, while the matter has been reviewed later by Stumpf¹³, and more recently by Stengel and Wolferth¹² and by Düntzer². Histological evidence has for the most part proved unsatisfactory in attempting to decide the origin of the lesions, for the picture in the reported cases is mainly that of an inflammatory process involving all the coats of the aorta and does not definitely indicate the site of the original focus of infection. Even that form of lesion which is usually regarded as the type of an embolic lesion^{3,7,9}, and which consists of a deep seated abscess or cavity opening on the surface by a narrow aperture can be as satisfactorily derived from a surface implanted focus (see *Case 17*). The general tendency, however, is to accept surface origin for those cases where the lesions lie within the range of contact

* Working on behalf of the Medical Research Council.

† See Lewis and Grant, *Heart*, 1923, X, 21. Five of the 31 cases there reported are omitted from the present series, two (*Cases 25 and 26*) being complicated by gross syphilitic aortitis, and three having been set up as museum specimens (*Cases 22, 23 and 24*). The identification of the cases of the present report with those previously described is noted in the text and in Table 1, page 33.

of the valvular vegetations (Marchand⁸, Richter¹⁰) and embolic origin for those situated more distantly (Eppinger³, McCrae⁷, Klotz⁴). Support is lent to the embolic theory by the facts that embolism of the smaller systemic vessels is a well-known occurrence in the course of an endocarditis, that the coronary arteries have occasionally been blocked and that their orifices are particularly favourably situated to receive particles broken off from the valvular vegetations. Also, there are certain rare cases of primary aortitis without a co-existing valvular endocarditis or a neighbouring extracardiac focus to account for them and which seem inexplicable except on the assumption that infection has arrived by way of the nutrient vessels, as for example, in the cases recorded by Stumpf¹³ and Scheuer¹¹. Further, it is held that the rapidity of the blood stream within the aorta, combined with the smoothness of its surface, would prevent infective material obtaining a foothold in the intima.

However, although embolism of the coronary arteries must be admitted as a possible cause of inflammatory lesions of the aorta, there are weighty considerations in favour of the alternative view. While a surface origin is easily acceptable for those lesions lying within the range of contact of vegetations attached to the aortic valve, it is not necessary to assume an embolic origin even for those lying beyond, for there is no real difficulty in allowing that the intima may be invaded by infective particles torn off from the valvular vegetations. The very rapidity of the blood stream in the aorta is a factor favouring such an invasion, for the more rapid the flow the greater will be the momentum of particles carried by it. Particularly a calcareous fragment projected in the systolic stream might readily abrade the aortic intima in passing. Further, this momentum is greater nearer the origin than higher up the aorta, and the increasing rarity of the lesions as the aorta is ascended, which has been commented on by almost all writers, is what would be expected from a surface invasion under these conditions. Eppinger³ has emphasised the multiplicity of the lesions within a small area as being strong evidence of their embolic nature, but this can be interpreted with equal force as evidence for a surface origin. From one point of view the group of lesions may arise by direct spread from one surface implanted focus; from another, it is to be remembered that the course of a subacute endocarditis may extend over many months, and in that time it is not difficult to imagine a succession of particles torn off from the valvular vegetations and giving rise to a circumscribed patch of lesions lying, so to speak, in the line of fire. Moreover, as will be seen later, such aortic lesions when examined histologically are found to be in different stages of development. Healing and active stages may lie side by side, a fact which is more in favour of successive intimal infections than of successive embolism of a circumscribed vascular territory. It is also to be considered that a possible explanation for some of those cases where the aortic lesions lie beyond the reach of valvular vegetations post-mortem is that the form of these vegetations has altered during the protracted course of the disease. Long

vegetations formerly present may have been so shortened by fragments broken off from them, by the contraction accompanying healing or by disintegration, that they may no longer reach the diseased area on the aorta. There is a further argument which would seem conclusive and which has apparently been neglected in the past. It is well known that aortic wall lesions are associated with an endocarditis of the left heart and lesions of the pulmonary artery with a right-sided endocarditis. So far as the writer can find there are no recorded cases of inflammation of the main pulmonary artery associated with a left-sided endocarditis without there being a simultaneous involvement of the pulmonary cusps or a patent ductus arteriosus to account for the spread of infection. When it is remembered that the coronary arteries in part supply not only the ascending aorta but also the main pulmonary artery with nutrient vessels, it must be admitted that the evidence is strongly in favour of surface origin for the aortic lesions. If they are of an embolic nature there is no evident reason why their seat of election should be the origin of the aorta to the exclusion of the pulmonary artery.

One point remains to be noted. It has been shown by Richter¹⁰ that the aorta may be involved not only by contact but also by a direct spread of the inflammatory process from the valves. However, as there is in most cases a healthy area lying between the diseased valves and the aortic lesions it would seem that this is not the usual mode of spread.

Apart from the aorta, contact lesions are generally held to occur in endocarditis; for instance, the lesions on the interventricular septum opposite a diseased aortic cusp of the mitral valve. The two following cases afford examples of vegetative lesions which cannot well be explained by the embolic theory and which illustrate spread by contact with remarkable clearness.

ILLUSTRATIONS OF SPREAD BY CONTACT.

CASE I.*

F. M., a night watchman, aged 43, was admitted to hospital on the 6th of July, 1922, diagnosed subacute infective endocarditis. He had always been healthy, and served for 22 years in the army, being discharged as time-expired in 1919. He first began to suffer from breathlessness on exertion in 1918, and this had gradually become worse. For a few months prior to admission there had been some swelling of the legs, a cough and a feeling of exhaustion. He had also been losing weight.

On admission there were signs of venous engorgement with enlargement of the liver, oedema of the legs and trunk, and congestion of the lungs. He was pale, the fingers were slightly clubbed and the spleen greatly enlarged and tender. There was a purpuric eruption on both legs. The heart was enlarged and diastolic and systolic murmurs were heard at the apex. The Wassermann reaction was positive, but several blood cultures yielded no growth of pathogenic organisms. The red blood cells numbered 3,660,000 per c. mm., the haemoglobin percentage was 44 and the colour index 0.6. The leucocyte count was 8,000 per c. mm.. The urine contained albumen, pus and red blood cells. The further course of the disease was characterised by the occurrence of Osler's nodes on the fingers, by a tender swelling of the dorsum of the right foot with cessation of the pulsation in the dorsalis pedis artery, and by a low irregular pyrexia. The heart failure gradually increased, and the patient died on the 19th of October, 1922.

* Case 32 of previous report.

Pathological changes.

Both lungs are congested and oedematous, and on section show numerous interstitial hemorrhages. The liver is enlarged and fatty. The *spleen* weighs 969 grammes and shows several infarcts. Both *kidneys* are of normal size, their surfaces are smooth and covered with minute hemorrhagic points. The *heart* weighs 482 grammes, both ventricles being hypertrophied. The *pulmonary artery* and valves of the right heart are normal. The *aortic cusps* are slightly thickened along their margins and the noduli are considerably enlarged. Along the ventricular surface of the cusps are a few scattered sessile vegetations.* The *aorta* is normal except for very small patches of atheroma at its base, specially along the ridges of the sinuses of Valsalva.

There are vegetations along the free edges of both cusps of the *mitral valve* which extend on to both the auricular and ventricular surfaces. The chordæ tendinæ are irregularly thickened and some large chordæ attached to the anterior cusp have been cut through near the valve margin and are enclosed in a great mass of partially calcified vegetations which hangs free in the ventricle (Fig. 4 *a*). A false chorda (*b*) extending from the ventricular septum to the middle of the more anterior portion of the posterior papillary muscle is incased throughout by minute vegetations. The base of the corresponding papillary muscle has a large patch of minute surface vegetations on it and a surrounding patch of thickened endocardium (*c*). There is a similar crescentic patch of vegetation on the hinder subdivision of the posterior papillary muscle (*e*). Low down on the septum where the wall joins the base of the posterior papillary muscle there are numbers of small vegetations arranged on the trabeculæ and false chordæ (*d*). When the free end of the cut chordæ covered with vegetations is swung round, it is found to come into contact with all the vegetations on the septal wall of the ventricle, of the false chorda, and with the two patches on the papillary muscle, the coincidence between areas of contact and surfaces involved by vegetation being remarkable in its detail: thus, the crescentic patch of vegetations *e* comes into contact with a knot-like protuberance of the vegetations surrounding the chorda *a*.

CASE 2.

J. P., a labourer, was admitted to hospital on the 23rd of August, 1922. No diagnosis was made during life, but post mortem examination revealed an infective endocarditis of the pulmonary valve. He had previously been healthy except for an attack of rheumatic fever 13 years before. Four months before admission he was seized with an attack of shivering and remained in bed for a month. Thereafter he complained of nausea and of vomiting after food and was able to eat and drink but little. His urine was sometimes of a red colour.

On admission he was seen to be somewhat emaciated and his complexion was of a waxy pallor. There were no signs of enlargement of the heart and no murmurs were detected at first, but later a to and fro murmur was heard once over the base of the heart. The lungs showed no sign of disease, and apart from rigidity in the epigastrium the abdomen was normal. The urine contained albumen and blood. A blood culture remained sterile. The red blood cells numbered 1,630,000 per c. mm., the hæmoglobin percentage was 30, and the colour index 0.9. The white cell count was 7,700 per c. mm. of which 89.5 per cent. were polymorphonuclears. The temperature was irregular, rising to 101° Fahr.. A week after admission an extensive ulceration of the left side of the palate developed. The irregular pyrexia continued, the patient gradually became weaker and died on the 4th of September, 1922.

* The aortic cusps were previously tabulated erroneously as being free from vegetations.

† This endocarditis, while subacute in its course, cannot be described as an instance of "subacute infective endocarditis," since this term would convey rather more than is intended.

Pathological changes.

There is a little clear fluid in both pleural cavities, the left lung is collapsed and the right congested and oedematous. The liver is normal in size and yellowish on section, while the spleen is large and soft. Both kidneys are increased in size, their surfaces smooth. The heart weighs 340 grammes. The valves of the left ventricle are slightly thickened, but otherwise normal. The aorta shows only very small patches of atheroma. The anterior cusp of the *tricuspid valve* is considerably thickened at its edge, but the remainder of the valve is comparatively healthy.

The pulmonary valve (Fig. 1) is extensively diseased. On the left posterior cusp is an area of flat vegetations spreading from the edge almost to the line of attachment on the ventricular surface. On the anterior cusp is one largish mass on the ventricular aspect ulcerating through in one spot. These vegetations are somewhat friable. On the edge of the right posterior cusp are masses of vegetation considerably calcified, and one of these masses projects in the form of a club-shaped polypus (*a*). In the sinus of this cusp, and on the base of the pulmonary artery, is a large patch of vegetations (*b*). These vegetations are more protuberant at the margins and thinner in the centre of the patch, which, as a whole, presents a concave surface toward the lumen, and the club-shaped vegetation, when tilted up, fits well into this concavity in which it had evidently lain during the heart's systole.

These two cases are clear examples of surface infection by contact, and it is noteworthy that the contact lesions are in the form of vegetations.

The distribution and form of vegetations on the aortic cusps was carefully noted in the 30 cases of the series, especially remarking the possibility of their contact with the aortic wall during systole. The aorta and sinuses in turn were closely scrutinised for inflammatory lesions and the position of these lesions was related to the area of contact of the valvular vegetations. All the lesions were submitted to histological examination with a view to tracing their stages of development, and for the same reason, portions of the aorta, apparently healthy, and also of the pulmonary artery, were studied microscopically. As a result, inflammatory lesions of the aorta and sinuses were found in half the cases. In all the 15 cases presenting such lesions, the aortic cusps were heavily involved by vegetations which, when placed in their systolic positions, could be brought into contact with the surface of the aorta. Of the 15 cases showing no lesion in these situations, there were no vegetations on the aortic cusps in 4, in 8 the vegetations were small and confined to the ventricular surfaces of the cusps, while in only 3 cases did the vegetations present possible areas of contact with the sinus walls; that is to say, of 18 cases in which the form and situation of the vegetations on the aortic cusps permitted contact with the aorta, lesions were found there in no less than 15. The inflammatory lesions of these 15 cases (see Table I, page 33) fall naturally into 3 groups, namely, vegetations, fissures and aneurisms, under which headings they will now be considered.

VEGETATIONS IN AORTA.

Vegetations in some form were present in all 15 of the cases showing inflammatory lesions of the aorta, but in 11 they were complicated by the presence of fissures and aneurisms. The 5 cases with vegetations only are as follows :—

CASE 3*.

C. R., a commercial traveller, aged 39, was admitted to hospital on the 31st of August, 1922, diagnosed subacute infective endocarditis. There was a doubtful rheumatic history in childhood, but otherwise he had been healthy until 1919, when he began to lose weight. Three weeks before admission he suffered from great shortness of breath and complained of swelling of the legs and of a sense of fullness in the abdomen.

On admission there were signs of advanced cardiac failure with orthopnoea and considerable enlargement of the liver. His colour was a dark tan with a yellowish tinge on the face and neck. There were a few petechial hemorrhages around the armpits and his fingers were clubbed, but the spleen was not palpable. The heart was slightly enlarged and a pronounced diastolic murmur was audible over the base. The urine contained albumen and red blood cells. The patient was too ill to admit of further examination, and he died three days later, the temperature having been subnormal since admission.

Pathological changes.

Both lungs are congested and in a state of brown induration. The liver is much enlarged and shows advanced nutmeg change. The *spleen* and *kidneys* are of almost normal size, but both show the scars of old infarcts. The *heart* is enlarged, both ventricles being hypertrophied and dilated. The *pulmonary artery* is normal as are also the valves of the right ventricle except for slight thickening. The *mitral valve* and its chordae are heavily involved by vegetations, the latter being reduced in number and thickened, while several are broken.

The aortic valve (Fig. 2) is also heavily involved by vegetations in which, however, no organisms are to be found.†

Commissure B is almost entirely destroyed, while commissure A is adherent for a length of 15 mm.. The left anterior cusp is marginally thickened, but there are only small vegetations along its line of apposition which have no area of contact with the sinus walls. No lesions can be found in this sinus. Long flat, firm vegetations hang from almost the whole of the free margins and lines of apposition of the right anterior and posterior cusps except towards commissures A and C where the cusp margins are thickened and rounded but free from vegetations. Beneath commissure B is a septal patch (V¹) of small vegetations and a small crescentic thickened fold of endocardium. The long anterior vegetation (V²) on the posterior cusp folds down and comes into accurate and natural apposition with the patch. In the upper part of the posterior sinus of Valsalva there are numerous small vegetations which are most closely grouped along the ridge of the sinus (V³). The area within which these sinus vegetations lie is found to coincide accurately with that covered by the long flat posterior vegetation (V³) attached to the cusp when it is turned upwards into its systolic position.

* Previously tabulated as Case 19.

† In this instance and in subsequent case reports this statement means that no collection of organisms could be found in sections stained by Gram, or by Murray's method (6th *Ser. Rep. of Imperial Cancer Research Fund*, 1919, 2nd method), although the vegetations were extensively explored.

There are no lesions in the right anterior sinus, though there is an area of contact within it. The aorta elsewhere is healthy.

As the three subsequent cases have already been fully reported and figured, only the relevant details will be described here. The patients were admitted with full clinical signs of subacute infective endocarditis, and this diagnosis was confirmed at autopsy. In each instance the pulmonary artery and valves of the right heart were normal and no organisms could be found in the vegetations on the mitral and aortic valves.

CASE 4.*

The vegetations on the left anterior cusp (L.A. in Fig. 17 of previous report) are seen to be confined to its ventricular surface and have no area of contact with the sinus. A small mass of vegetations projects from the centre of the margin of the right anterior cusp, but there are no vegetations on the sinus wall. There are similar projecting vegetations on the margin of the posterior cusp, and in the area of contact on the sinus wall near commissure C there is a small group of vegetations lying just beneath the ridge of the sinus.

CASE 5.†

On re-examining this specimen, pendulous vegetations are seen attached to both the posterior and left anterior cusps (Fig. 18 of previous report), and these have areas of contact in their respective sinuses, which, however, are healthy. In the right anterior sinus there is a patch of vegetations and erosion around the mouth of the right coronary artery, and this lies within the area of contact of vegetations which project from the margin of the right anterior cusp near commissure B. The aorta shows slight atheroma but is otherwise healthy.

CASE 6.‡

The aortic valve is congenitally bicuspid, and both the posterior and the combined right and left anterior cusps are seen to be covered with vegetations on their ventricular surfaces. The vegetations extend on to the sinus side of the posterior cusp towards commissure C and on the underlying sinus wall there is a small group of vegetations (not visible in the figure). Elsewhere the sinuses are healthy, but vegetations extend from the combined cusps on to the ridge of the fused commissure A. The aorta is free from disease.

Case 7 is particularly interesting in that the vegetative lesions in the sinus, being well advanced towards healing, are invisible to the naked eye and were only discovered on microscopic examination.

* Previously reported as *Case 5*.

† Previously reported as *Case 6*.

‡ Previously reported as *Case 11*, and illustrated in Fig. 23.

CASE 7.*

W. B., a clerk, aged 30, came under observation for subacute infective endocarditis on the 2nd of December, 1920. Previously healthy, he enlisted in 1915, but during training complained of shortness of breath and palpitation. He was wounded in France, 1916, and discharged from the Army in 1917. A few weeks before coming under observation his symptoms had become worse.

On examination his exercise tolerance was only fair. The heart was moderately enlarged and diastolic murmurs were audible at apex and base. The fingers were conspicuously clubbed, but the patient stated that they had been so since childhood. The spleen was palpable. The red blood cells numbered 5,720,000 per c. mm., the haemoglobin percentage was 82 and the colour index 0.7. The leucocyte was 10,400 per c. mm.. His condition remained stationary till September, 1922, when, owing to the onset of cardiac failure he was admitted to hospital on the 16th of that month. The urine was then found to contain albumen and red blood cells, but no blood culture was made. The temperature remained for the most part subnormal, and the cardiac failure increasing, the patient died on the 26th of September, 10 days after admission.

Pathological changes.

The lungs are congested and the left lower lobe is consolidated. The liver is large, soft and fatty. The *kidneys* are of normal size and show the scars of old infarcts, while on section a few completely, but no partially, hyalinised glomeruli are to be found. The *heart* weighs 567 grammes, both ventricles being hypertrophied and dilated. The *pulmonary artery* is normal, but there is some thickening of the pulmonary and tricuspid valves, especially of the latter. The *mitral valve* is greatly thickened, and both flaps show numerous vegetations. There are several endocardial thickenings on the interventricular septum beneath the aortic valve (Fig. 9, μ^1 μ^2 μ^3).

All the cusps of the aortic valve are marginally thickened and the commissures adherent. The right and left anterior cusps are involved by firm, low and partly calcified vegetations confined to the upper part of their ventricular surface and having no area of contact with the underlying sinuses. The posterior cusp is similarly involved, but the vegetations extend just over the free margin, and at its centre become pendulous and considerably calcified (Fig. 9, V). When placed in their systolic position the projecting vegetations have an area of contact over the upper part of the central portion of the posterior sinus. The sinus wall in this situation appears normal, but in serial sections several small nearly healed vegetations are found scattered over the surface. Other portions of the same and of the remaining sinuses, similarly examined, show no lesions, and the aorta itself is healthy. No organisms are to be seen in the vegetations.

Histologically, the aortic vegetations of these cases do not differ from those found on the valves of the heart and consist essentially of a ground work of thrombotic material which may contain organisms, and which is more or less invaded from its base by young connective tissue. In shape they may be small cauliflower-like growths, or flat and spread over a wider surface. They may disturb the intima only or may involve the aortic wall more deeply, and are accompanied by a greater or less inflammatory reaction in the neighbouring media and adventitia. The appearances, however, are very various according to the severity of the infection and according to the degree in which protective or reparative processes have pursued their course.

* Previously tabulated as Case 16.

While, on the other hand, the picture may be mainly that of advancing infection, and while on the other, the reparative processes may predominate, the impression is commonly that of a long drawn out struggle between these two forces, resulting in an area of chronic productive inflammation involving the whole thickness of the aortic wall.

An example of an early vegetation containing organisms is illustrated in Fig. 11. The thrombus cap is crowded with Gram-positive cocci (*b, b, b*), while from beneath it is being invaded by numerous fibroblasts, large wandering cells, a few giant cells (*G.C.*),* many binuclear or trinuclear wandering cells, and some mononuclear and polymorphonuclear leucocytes. The base of the vegetation rests on the internal elastic lamina, and at one point this and the underlying superficial laminae have been broken through and their ends carried into the base of the vegetation, while the neighbouring laminae are slightly separated by a proliferation of the connective tissue cells lying between them together with a few leucocytes. The underlying media and adventitia are undisturbed.

When infection has the upper hand, the further course of such a lesion is marked by an extension of the inflammatory process. The centre of the vegetation breaks down and the involvement of the media proceeds to an ever increasing depth and extension. Between the underlying and neighbouring elastic laminae there is a progressively denser infiltration by leucocytes even up to the formation of an abscess, the formed elements undergoing necrosis, the elastic laminae themselves resisting for a long time. The adventitia also shares in the inflammatory process, and ultimately, as will be seen later, the aortic wall gives way. Throughout this process there is always some attempt at repair, as evidenced by the presence of fibroblasts, and in some specimens the appearances are those of a lesion advancing to complete healing. Such a condition is illustrated in Fig. 13. Here the media has been penetrated and destroyed to almost half its thickness, but the wide breach in the elastic media is repaired by a growth of connective tissue, the cells of which lie more or less in layers parallel to the surface. A few lymphocytes (*l*) are to be seen at the base of the scar which is everywhere pervaded by fine newly formed elastic fibrils. The media and adventitia beneath show little change, the only evidence of disturbance being a sparse collection of lymphocytes around the vessels in the outer third of the media. There remains, however, an intermediate type of vegetative lesion in which neither infection nor repair has definitely gained the upper hand. The vegetations in such are usually low and spread over a considerable area. The thrombus cap may be dense, hyaline and partly calcified, or may be entirely organised by young connective tissue which may show areas of necrosis. Organisms are not usually to be seen. The intima between the vegetations may be thickened

* Incidentally it may be stated that giant cells are to be found in the basal portions of vegetations in nearly every case of subacute infective endocarditis.

by an increase of its connective tissue or it may be replaced by a necrotic surface in which the underlying elastic laminae are exposed. In the media beneath the vessels are prominent and are found to penetrate beyond the outer third. Lymphocytes and plasma cells are to be seen collected round them, and in their neighbourhood the elastic laminae may be disturbed and even broken by areas of proliferating connective tissue cells. There may also be some degeneration of the formed elements, the media as a whole having a somewhat patchy appearance. The adventitia is usually thickened by an increase of its connective tissue, and many fibroblasts are to be seen together with a sparse diffuse infiltration of lymphocytes and plasma cells, while many of the vessels show an advanced degree of obliterative endarteritis.

A routine microscopic examination of the apparently healthy sinus and aortic wall and of the pulmonary artery in these cases revealed no significant changes. Beyond some intimal thickening of the vasa vasorum and the presence of a few lymphocytes along their courses no sign of inflammatory reaction could be found which would indicate a process of embolism in these vessels. Such lesions as were found are also to be seen in what are usually described as normal hearts from patients of a similar age.

From the description of these five cases it is apparent that the vegetative lesions on the aorta and sinuses are present only in those regions which can be covered by vegetations attached to the aortic valves, though lesions have not formed in every area of contact, as, for example, in the right anterior sinus of *Case 3*, yet when they do occur they show such a definite relation to the vegetations on the aortic cusps that it seems justifiable to conclude that they have arisen through surface infection implanted by contact. The histological picture is in agreement with this view, and it has been shown that all intermediate stages can be traced from an early surface lesion beneath which the aortic wall is undisturbed to either an extensive deep invasion or a healed scar.

FISSURES OF AORTA.

Among the less conspicuous lesions of the sinuses and aorta there is one type to which, so far as the writer is aware, attention has not hitherto been directed, namely minute, linear or radiate fissures. Various forms of tears or rupture of the aorta have frequently been reported. Osler⁶ and McCrae⁷ mention cracks in connection with underlying aneurisms, but the writer has been unable to find descriptions corresponding to the minute lesions which have been observed in 6 cases of the series as follows.

CASE 8.*

J. H., a professional soldier, aged 42, first came under observation on October the 17th, 1921. Except for remittent fever in 1897 and rheumatism in 1900, he had previously been healthy, and was discharged from the army as time expired in 1913. He then began work as a plumber, but ultimately had to give it up on account of shortness of breath and palpitation on exertion. In August, 1921, he suffered from a painful swelling of the calf of the right leg, and by this time his symptoms had become worse.

* Previously tabulated as *Case 17*.

On examination the patient showed signs of venous congestion with oedema of the shins. He was pale, the spleen was palpable and the pads of the fingers were a little bigger than usual. The heart was enlarged, a to and fro murmur was audible over the aortic cartilage, and the pulse was slightly water hammer in type. A diagnosis of suspected subacute infective endocarditis was made, and later, on March the 22nd, 1922, subsequent to the onset of cardiac failure, the patient was admitted to hospital. He was then too ill to admit of a thorough examination, and died a few days later.

Pathological changes.

Both lungs are congested and there is a small quantity of clear fluid in each pleural cavity. The liver is normal in size, but on section shows nutmeg changes. The spleen weighs 567 grammes, is firm but not infarcted. Both kidneys are large and show several depressed scars from old infarcts. The heart weighs 823 grammes, both ventricles being hypertrophied and dilated. The pulmonary artery and valves of the right heart are normal. The mitral valve is thickened at its edges, and there is a large patch of vegetations on the ventricular surface of the aortic flap. There are several crescentic endocardial thickenings (Fig. 8 *l*, *t*) on the interventricular septum beneath the aortic valve. No organisms are to be found in the vegetations.

The aortic cusps (Fig. 8) are extensively diseased, commissure A being completely, and commissure B slightly adherent, while commissure C is filled with vegetations. The line of apposition of the right anterior cusp is covered with vegetations. These have no area of contact in the sinus, which is healthy except for a small nodule of atheroma (*n*). The left anterior cusp has similar vegetations, but at the centre of the cusp they extend on to its margin (*V*¹) and over on to its sinus aspect, though there are no lesions in the area of contact. Each end of the posterior cusp is covered with vegetations, especially near commissure C, where a large mass of calcified vegetations (*V*²) projects from the margin. Within the area of contact of this mass in the upper half of the posterior sinus is a small break in the surface about 2 mm. long by 1 mm. wide (*f*). It is stellate in appearance, being widest at its centre from which fine fissures extend outwards. The surface of the sinus immediately surrounding it is slightly roughened and granular.

Microscopically the fissure is seen to extend two-thirds through the elastic coat of the sinus wall, which is here 1 mm. thick. At its centre it is U-shaped and from the sides of the U several narrow cracks extend outwards, gradually lessening in depth. The edges of the fissures are slightly irregular and covered with a thin layer of necrotic material in which lie the severed ends of the medial elastic laminae. The granular appearance of the surface in this region is due to the presence of small flat vegetations which are more or less completely organised. These vegetations are for the most part quite superficial, the internal elastic lamina of the media extending unbrokenly beneath them except for one or two small breaches where the vegetations have penetrated rather more deeply. At the sides of the main fissure the elastic laminae are separated by numerous spindle-shaped connective tissue cells with large nuclei, and there is a diffuse lymphocytic infiltration, particularly between the deeper lying laminae. The adventitia is congested and diffusely infiltrated with lymphocytes and plasma cells.

CASE 9.*

J. P., a newsagent, aged 39, was admitted to hospital on the 27th of March, 1922, diagnosed subacute infective endocarditis. Previously he had been healthy and served 8 years in the army. Fifteen months before admission he began to complain of shortness of breath and this gradually became worse.

On admission there were signs of venous engorgement with congestion of the lungs. He was pale and the fingers were clubbed, though the spleen was not palpable. The heart was enlarged and systolic and diastolic murmurs were heard over the apex and base. The pulse was water hammer in type. A blood culture remained sterile. The urine contained red blood cells. There was no pyrexia. The heart failure increased and the patient died on the 6th of April, 1922.

Pathological changes.

Both lungs are congested and oedematous. The liver shows a moderate degree of nutmeg change. The spleen weighs 425 grammes and is infarcted. Both kidneys are large but not infarcted and their surfaces are smooth. The heart weighs 765 grammes, both right and left ventricles being greatly hypertrophied. The pulmonary artery and valves of the right heart are normal. Both flaps of the mitral valve are involved by vegetations which extend on to the chordæ tendineæ.

All the aortic cusps are completely covered from attachment to margin on their ventricular surfaces with firm and calcareous vegetations which extend over the margins on to the sinus aspects and have areas of contact with the walls of all three sinuses of Valsalva. No organisms are found in the vegetations. The vegetations also involve the commissures, and there is an aneurism running up under commissure C behind the wall of the aorta and between it and the wall of the left auricular appendix. The coronary arteries arise normally. The aorta above the edges of the sinuses of Valsalva is normal except for a few patches of atheroma especially on the ridges themselves. Below the ridges there are scattered vegetations on the walls of all three sinuses, most numerous, however, and most closely grouped in the posterior sinus, and in each sinus the vegetations lie within the areas of contact of the valve vegetations.

Through the group of vegetations in, and about half way down, the posterior sinus is a very narrow longitudinally lying linear fissure, 2 to 3 millimetres in length. Sections through this region of the sinus wall show that the intima is enormously thickened by young connective tissue which forms the base of small organising vegetations and which is diffusely infiltrated by polymorphonuclear leucocytes, lymphocytes and plasma cells. In parts the deeper layers of this tissue are vascularised by vessels extending through the media, and these vessels are surrounded by collections of inflammatory cells of the same types. Beneath this thickening, the superficial elastic laminae run unbrokenly, but they are opened out and appear separated by young connective tissue cells. The middle and deep parts of the media are very vascular and much infiltrated by inflammatory cells which are most densely grouped around the vessels. The adventitia under this region is thick and dense, and is very vascular. It is infiltrated in a similar manner

* Previously tabulated as Case 20.

and shows deposits of hemosiderin. The vessels show all degrees of obliterative endarteritis. The fissure extends through the thickened surface layer and halfway through the elastic laminae of the media where it expands slightly and is filled by recent blood clot. Its walls are covered with a thin layer of necrotic material, in which the severed elastic laminae end.

As the remaining four cases in this section (cases 10-13) have already been fully reported, only the relevant details require to be added. They were admitted with full physical signs of subacute infective endocarditis, a diagnosis which was confirmed post-mortem. The disease in each instance involved the aortic and mitral valves while the valves of the right heart and the pulmonary artery were normal. No organisms were to be seen in sections of the vegetations.

CASE 10.*

The aortic valve (Fig. 5) is congenitally bicuspid, commissure A being reduced to a smooth low ridge and the right and left anterior cusps thrown into one. The edge of the combined cusp is thickened and smooth, and there are large flat vegetations attached to its ventricular surface about its middle. These vegetations here extend over the margin a little way on to the sinus side of the cusp and between this point and commissure B there is a pendulous vegetation 17 mm. long, attached to the cusp margin. The posterior cusp is similarly thickened and it is torn about its middle. Large flat vegetations are also attached to its ventricular surface and to the anterior margin of the tear. The vegetations are firmly attached and tough. On section they are seen to be considerably organised from their bases: they contain many deposits of lime salts and no organisms are to be found in them. On the base of the aorta, above and to the right and left of commissure A, are two small tri-radiate fissures (Fig. 5 *f*, *f*), each about 2 mm. long and 0.5 mm. wide. The intimal surface round these lesions appears slightly roughened, but elsewhere the aorta and sinuses of Valsalva, except for a few small and scattered atheromatous patches, are smooth and normal in appearance. The end of the long pendulous vegetation when tilted upwards comes into apposition with the two fissures. There are no lesions in the posterior sinus, although the valvular vegetations on the posterior cusp have an area of contact. Serial sections were cut of both fissures and adjoining aortic wall. In parts the intima has disappeared leaving a necrotic area in which the superficial elastic laminae of the media are exposed. In the other parts the intima is irregularly thickened by a growth of young connective tissue, the cells of which are arranged more or less parallelly. Attached to the surface here and there are tags of thrombotic material, in which, however, no organisms are to be found. The internal elastic lamina extends for the most part unbrokenly beneath this new connective tissue, but occasionally it and the underlying superficial laminae are penetrated and

* Previously reported as *Case 10* (Fig. 22).

interrupted. The connective tissue varies in age; in parts it consists of succulent fibroblasts, while in others it is denser and older and pervaded by fine elastic fibrils, the whole appearance being that of healing vegetations in various stages of organisation.

The aortic media shows a considerable patchy disturbance due to collections of young connective tissue cells together with a few lymphocytes lying between and separating and even interrupting the elastic laminae. Usually small blood vessels are to be seen in these areas, and many vessels enter the media from the adventitia penetrating about half its thickness. There is a general increase in the connective tissue elements between the elastic laminae, and many of the cells and muscle fibres show granular degeneration. There is also a diffuse but sparse infiltration with lymphocytes. The adventitia also is more vascular than normal and is infiltrated with lymphocytes and plasma cells. Many of the vessels show proliferation of the intimal lining up to actual obliteration of their lumina, and some of them are surrounded by lymphocytic collections. There is also some proliferation of the adventitial connective tissue specially at its junction with the media where in parts it resembles granulation tissue. Through this inflamed and degenerate area two fissures extend, the one almost, and the other completely, through the media at their deepest parts. They are V-shaped in section, their margins slightly irregular and covered with a thin amorphous layer of necrotic material staining a bright red with eosin and in which the elastic laminae of the media are sharply broken off. They are otherwise unlined except about the centre of the left hand crack where a healing vegetation, which lies on the surface, extends a little way down into the fissure. No organisms can be found in the serial sections or in the valve vegetations.

CASE 11.*

The aortic valve is severely diseased and is congenitally bicuspid. The aorta and sinuses of Valsalva above the thickened bases of the cusps are seen to be free from disease except about the middle of the posterior sinus where a small vegetation is seated, and along the lower edge of which runs a minute fissure partly overhung by the vegetation (seen immediately below the *A* of *L. A.* in Fig. 20 of previous report). This fissure and vegetation are covered by the projecting vegetation attached to the margin of the left anterior cusp. Serial sections of the sinus wall containing the fissure show on the intimal surface several low vegetations which are almost completely organised by young connective tissue, and which involve only the intimal layer of the sinus wall without penetrating the elastic laminae of the media. The media itself is diffusely but sparsely infiltrated with inflammatory cells, chiefly lymphocytes. The adventitia is thickened and much more densely

* Previously reported as *Case 8*.

infiltrated with lymphocytes and plasma cells. It also shows scattered deposits of hemosiderin. Through this area the fissure extends, at its deepest part, more than half way through the elastic laminae of the media, but towards the extremities it lessens in depth and is merged with the surface vegetations. In section the fissure is somewhat crescentic in shape and curves laterally through the elastic laminae, undercutting a portion of the aortic wall. This undercut portion projects slightly from the surface and is partly necrotic, the elastic laminae in it being much fragmented. The fissure itself contains some recent blood clot and it is unlined by granulation tissue, its walls being formed of a thin layer of necrotic material in which no organisms are found.

It is apparent from the above description that in each of the four cases the wall of the aorta in the neighbourhood of the fissures is in a state of chronic productive inflammation. On the surface the intima is eroded or is replaced by vegetations in varying stages of organisation. The media is more or less infiltrated by mononuclear cells, particularly along the line of the vessels entering it from the adventitia. There is also an increase in the number of the connective tissue cells between the elastic laminae which themselves may be loosened out or even interrupted, while there is in places a patchy degeneration of the muscular elements. The adventitia is more vascular than normal, and many of the vessels show obliterative endarteritis. There is a varying degree of proliferation of the adventitial connective tissue and at the same time a diffuse and perivascular infiltration by lymphocytes and plasma cells. These appearances are exactly those which have been described for the intermediate type of vegetative lesion, and the relations of the damaged areas to valve vegetations indicates that they have originated in the same manner. Given such an area of the aortic wall damaged by chronic inflammation, it is not difficult to understand it giving way under the stress of systole and producing the small fissures just described. In addition, however, there is another factor which may assist in producing the rupture. For example, as has been seen, in *Case 10*, the long pendulous vegetation attached to the right anterior cusp when tilted upwards covers the area in which the fissures lie, and the valve vegetations are not only firm and tough, but also partly calcified. It is possible that the systolic impact of the valve vegetation with the base of the aorta may not only cause the area of damage through surface infection, but may later aid in its rupture. This mode of origin has been suggested by Libman⁶ for small aortic aneurisms, and has been compared by McCrae⁷ to the production of a clean cut wound of the scalp under the impact of a blunt instrument.

As with the vegetative lesions, the following cases illustrate that with the fissures too, healing may take place, since all transitions can be found from those just described with raw sharply cut margins to those which are completely filled up by new connective tissue.

CASE 12.*

The aortic valve is congenitally bicuspid, commissure A being absent and both cusps encased in thick rough but firm vegetations which extend for some way down both ventricular and sinus aspects of the cusps. The aorta above the sinuses seems to be normal, but both sinuses of Valsalva are much diseased in their upper parts, the surface being eroded or occupied by vegetations. In the posterior sinus a small fissure is seen near the cusp's attachment. In the combined sinus between the mouths of the coronary arteries is a vertical fissure 5 mm. long surrounded by small protuberances, which on section are found to be almost completely organised vegetations. The media in this region shows the patchy disturbance already described, and the vessels entering it from the adventitia are surrounded by lymphocytes and fibroblasts. In the adventitia is a diffuse and perivascular infiltration by lymphocytes and plasma cells, and many of the vessels show a considerable degree of obliterative endarteritis. The fissure which passes across this area is wider than it is deep, and extends about one-third through the medial coat of the wall. Its base is flat, its sides somewhat convex and its lower angles slightly undercut the elastic laminae which appear sharply cut across. So far the description agrees with that of the other fissures, but in this instance the breach is lined and partly filled up with a growth of young connective tissue continuous with that of the intima and the vegetations upon it.

CASE 13.†

The aortic valve (Fig. 6) is congenitally bicuspid, commissure A being absent. The posterior cusp on its ventricular surface is covered with vegetation which extend on to its sinus aspect towards commissure C, and which there have an area of contact with the wall of the posterior sinus. In this area of the sinus wall, which is elsewhere free from disease, there is a small group of vegetations across which a small vertical fissure extends. The combined right and left anterior cusps are almost entirely replaced by masses of vegetations partly calcified and for the most part in an advanced state of organisation. The sinus wall behind this cusp is much diseased. Below the mouth of the right coronary artery is the smooth and rounded opening of a sinus aneurism (A²) about 2 cm. in depth containing laminated clot and burrowing into the muscle of the infundibulum. Below the orifice of the left coronary artery is a second aneurism (A¹) complex in outline partly filled with clot, and projecting into the space between aorta and left auricular appendix. Running down the centre of the sinus is a series of small fissures (*f*) composed of a main vertical, irregularly linear fissure from which lateral branches extend.

* Case 12 and Fig. 24 of previous report.

† Reported previously as Case 7 (Fig. 19).

The series of fissures in the combined sinus is interesting in that it shows a combination of the lined and unlined conditions. In serial sections the main vertical fissure extends almost completely through the elastic laminae, but its lumen is, except for a narrow channel, completely filled by a growth of young connective tissue, the cells of which are not yet arranged in parallel rows, but are for the most part vertical to its surface. The subsidiary fissures extending from it are unlined by connective tissue and their margins are covered with the thin necrotic layer described in previous cases. The transition from the one picture to the other is sharp and is illustrated in Fig. 10. The intimal surface in the neighbourhood of the fissures is eroded and necrotic, in places the internal elastic lamina is absent and the underlying elastic fibres are exposed. As in the other cases the media (*Am.*) and adventitia (*Ad.*) are greatly disturbed. Round the lined fissure (*f*¹) large numbers of fibroblasts and inflammatory cells lie between the elastic laminae, which are opened out and separated, but in the case of the unlined fissure (*f*²) this condition is almost absent. The media generally shows the patchy disturbance described above and is diffusely infiltrated with lymphocytes. The adventitia beneath is dense and vascular, and many of the vessels show obliterative endarteritis. It contains many fibroblasts, lymphocytes and plasma cells, all of which are specially grouped round the smaller blood vessels. The central lined fissure is apparently the older lesion in which healing is taking place and the unlined fissures are more recent lateral extensions. The diseased area of the posterior sinus wall shows the same advanced grade of chronic inflammation, and the vegetations are flat and considerably organised. The fissure there extends through one-third of the thickness of the elastic media and is lined and partly filled up by young connective tissue. Lying to one side of this fissure and parallel to it is another linear breach of the media which was not visible to the naked eye. It is deepest at its centre, fades off towards its extremities and is entirely filled by connective tissue (Fig. 12). At its centre almost the entire thickness of the media is penetrated, only the fragmented remains of the deepest laminae being found across the base of the scar. The ends of the severed laminae are also somewhat fragmented and the more superficial ones are curved inwards over the deeper. The connective tissue filling the gap is denser at its base and pervaded by fine elastic fibrils, but superficially it is looser and composed of succulent fibroblasts. This fissure represents a much later stage of healing and is comparable to the healed vegetations earlier described.

It remains to be added that microscopical examination of the pulmonary arteries and the healthy portions of the aorta and sinuses of these six cases showed no significant changes.

Thus the fissures have been brought into line with, and are to be considered as a result of, the vegetative lesions, which in these additional cases also seem to have arisen from surface infection.

ANEURISMS OF AORTA.

Aneurisms have been found in 5 of the 15 cases showing inflammatory lesions in the aorta and sinuses. As with the vegetations, so with the aneurisms, the appearances vary greatly according to the severity of the infection and the degree of repair which has taken place. Case 14 is an illustration of the more acute type of aneurism.

CASE 14.

C. G., a warehouseman, aged 28, was admitted to hospital on the 29th of January, 1923, diagnosed subacute infective endocarditis. Always healthy, he served in the war as a fit man and was interned in Holland from 1914-1918. In August, 1922, he had an attack of "influenza" with pain in the limbs, and afterwards suffered from palpitation and breathlessness on exertion, together with swelling of the ankles.

On admission he showed signs of venous congestion with enlargement of the liver. He was pale, the fingers were very slightly clubbed and the spleen was palpable. The heart was slightly enlarged, a diastolic murmur was heard near the apex and base and the pulse was water-hammer in type. The urine contained albumen and red blood cells. A blood culture yielded a growth of streptococci. The temperature was irregular, rising occasionally to 102 degrees, but remaining mostly between 99 degrees and 101 degrees with frequent remissions. The patient remained in much the same condition, complaining of pains all over the body. In the beginning of April his throat became very sore and there was a thick yellowish fluid discharged from his left ear. Signs of pneumonia developed and he died on the 6th of April, 1923.

Pathological changes.

There is a quantity of clear fluid in each pleural cavity and the lower lobes of both lungs are consolidated. The *spleen* is enlarged and contains several infarcts. The *kidneys* are enlarged and have the pale swollen fatty appearance of parenchymatous nephritis. On the right kidney is an old infarct. The larynx shows several small superficial ulcers and the middle ear on the left side contains pus. The *heart* weighs 378 grammes. The *pulmonary artery* and valves of the right ventricle are normal. There are vegetations on both surfaces of the aortic flap of the *mitral valve*.

The *aortic valve* is bicuspid, commissure A being represented by a fibrous ridge and the right and left anterior cusps thrown into one. There are numerous vegetations along the margins and lines of apposition of the combined cusps, and in the region of the fused commissure these are pendulous. The sinus walls behind these cusps are healthy, but just above the ridge of the left anterior sinus, a little above and to the left of commissure A, is the mouth of an aneurism 0.5 cm. in diameter with fissured edges and surrounded by low vegetations. There are a few small vegetations also round the orifice of the left coronary artery. The aneurism and vegetations are covered by the pendulous vegetations on the valve when they are tilted into their systolic position. The posterior cusp is thickened and there are low vegetations on nearly the whole of the ventricular surface. These extend on to the sinus side of the cusp towards commissure C, and have an area of contact on the sinus wall just below the ridge of the sinus. Here lie several small vegetations. The sinuses of Valsalva and the aorta elsewhere are healthy except for a few scattered atheromatous deposits. Numerous gram positive cocci are present in all the lesions. Microscopically, the aperture in the aorta is found to lead into a shallow irregular aneurism undercutting the media. The sac wall is

formed mainly by thickened adventitia and the prolongations of the cavity are filled by recent blood clot. In some parts the wall is necrotic and breaking down and contains numerous organisms: in the other an active process of repair is going on, as evidenced by the vascularity and the presence of succulent fibroblasts. Frequent giant cells are also to be seen in this granulation tissue. The wall, as a whole, is diffusely infiltrated by polymorphonuclear and mononuclear leucocytes together with very numerous plasma cells. The mouth passes through the severed elastic laminae of the media which are curved over inwards towards the sac and covered by a low growth of connective tissue necrotic in parts and here containing organisms. The intima surrounding the mouth is thickened, and on it are seated low vegetations which erode the superficial laminae and are partially organised from their bases. The surfaces of these vegetations contain numerous clumps of cocci. The aortic wall beyond this area is healthy.

In this case there is no need to look to embolism of the vasa vasorum as the factor underlying the formation of the aneurism. Like the other lesions described, it lies within the area of contact of a valvular vegetation and the histological appearances, as will be seen from *Case 17*, in which there is a very similar aneurism, are quite compatible with a further stage of the evolution of a vegetative lesion where infection has the upper hand.

The two aneurisms described in *Case 13* present a somewhat similar picture, but in this instance there is a greater degree of healing. Sections of the mouth and wall of the aneurism, marked *A*² (Fig. 6), shows that it is composed of firm old standing fibrous tissue diffusely infiltrated with mononuclear leucocytes and pervaded by fine elastic fibrils. The laminated clot which lines it is partially organised, and the intima surrounding the mouth of the aneurism is irregularly thickened by new connective tissue. No organisms can be found in this lesion. In this case also the aneurisms lie within areas of contact, and their association with other lesions in the same situation indicate their origin from surface infection. These two aneurisms correspond to the usual description of the so-called "chronic" mycotic aneurisms. They can be considered either as representing a later and healing stage of an acute aneurism like that just described, or as having been "chronic" from their commencement. This latter origin is suggested by their association in *Case 13* with fissures of the sinus. The conditions found in the fissured lesions are all that are necessary for the formation of an aneurism; indeed the fissures themselves might be classified under this term, and it is obviously possible that the aneurisms may have arisen by an extension of similar breaches of the sinus wall, or as a result of the giving way of the scars which have also been described.

Two further cases were found to display aneurisms in the sinuses of Valsalva.

CASE 15.*

W. A., a builder, aged 38, was admitted to hospital on the 17th of May, 1920, diagnosed subacute infective endocarditis. Previously healthy, except for an attack of rheumatic fever 13 years before, he enlisted in 1916, and was discharged in 1919 on account of a bullet wound in right forearm. During his service he had frequent attacks of precordial pain, especially on exertion, and this had recently become worse; in addition he suffered from violent attacks of vomiting with pain over the epigastrium.

On admission his exercise tolerance was poor and the veins of the neck were full. He was pale, his fingers were clubbed and the spleen palpable. The heart was enlarged and systolic and diastolic murmurs were audible over the apex and base. The Wassermann reaction was negative and blood cultures remained sterile. The red blood cells numbered 5,400,000 per cmm., the hæmoglobin percentage was 50 and the colour index 0.5. The leucocyte count was 3,500 per cmm. The urine contained albumen and red blood cells. There was an irregular low pyrexia, and the further course of the illness was marked by increasing heart failure from which the patient died on the 29th August, 1920.

Pathological changes.

Both lungs are congested and cedematous and the liver shows nutmeg change. The kidneys are congested and of a mottled appearance, but are not infarcted. The spleen shows one large old infarct. The heart is enlarged, the left ventricle especially being hypertrophied. The pulmonary artery and valves of the left heart are normal. The mitral and aortic valves are extensively involved by vegetations.

The left anterior cusp of the aortic valve (Fig. 3) is thickened especially in the left two-thirds of its margin. The ventricular surface of the right third is covered with vegetations which do not extend to the sinus aspect of the cusp except where they perforate the line of attachment in one small area. The sinus of the cusp is healthy. Vegetations cover the whole of the upper part of the ventricular and sinus surfaces of the right anterior cusp and have an area of contact on the sinus wall along a level below the mouth of the right coronary artery, but no lesion can be found within it. The posterior cusp is similarly involved but the vegetations extend further down the sinus side and project more from the cusp margin and their area of contact includes almost the whole of the posterior sinus of Valsalva. In this sinus are scattered minute vegetations (*v*) and the smooth rounded opening of an aneurism (*a*) which lies in the posterior part and undermines the thickened cusp. Numerous gram positive organisms are present on the surfaces of the vegetations. Microscopically, the aneurismal sac is composed of dense fibrous tissue containing fine elastic fibrils, and it is lined by partially organised blood clot. The capsule is continuous with the greatly thickened intima surrounding the mouth on which there are low vegetations, and beneath which the elastic fibres of the media of the sinus wall are curved over inwards. At various points in the capsule an active inflammatory process is going on and organisms are found in large numbers in the outer layers of blood clot in the sac.

As the next case has already been fully described and figured, additional details only are given.

* Previously tabulated as Case 18.

CASE 16.*

E. U., a male, aged 33, was admitted with full physical signs of subacute infective endocarditis and this diagnosis was confirmed at autopsy. The pulmonary artery is normal and the valves of the right ventricle present no significant change. There are a few vegetations on the mitral valve.

The combined right anterior and posterior cusps of the congenitally bicuspid aortic valve are covered with calcified projecting vegetations and having an area of contact along the upper part of the combined sinuses. In the posterior part of the combined sinus there is the mouth of a shallow aneurism lying near the base of the cusp towards commissure C. Elsewhere the sinus wall is apparently normal, but serial sections of the area of contact reveal the presence of scattered low healing and healed vegetations. One of the latter has been described on page 17 of this report, and is illustrated in Fig. 13. The left anterior cusp is perforated by vegetations at each end just below the margin and the underlying sinus wall in both areas shows minute vegetations. The aorta and sinuses elsewhere are normal and no organisms are found in the vegetations. These two cases offer additional illustrations of vegetative lesions within areas of contact of valvular vegetations. The aneurisms may possibly also have arisen by contact, but their situation close to, and undermining, the bases of the cusps indicates rather that they are due to a direct extension by continuity of the disease process from the cusps.

In connection with the origin of such aneurisms there is an interesting point to be noted in passing. Babes¹ and others have commented on the association between aneurism and a bicuspid condition of the aortic valve such as is seen in *Cases* 13 and 16. In certain instances the aneurism has been attributed to a "Bildungsanomalie" and interpreted as confirmatory evidence of the congenital origin of the bicuspid valve. For example, in a case described by Babes (*Case* 3), in which there was an aortic aneurism and rupture, the right anterior and posterior cusps were found to be fused without trace of subdivision while the cusps themselves were thin, transparent and elastic. There is no doubt that the bicuspid condition in this case was congenital, and it seems quite possible that it was associated with a congenital defect in the strength of the aortic wall. In a second case (*Case* 1) the truth of his explanation is more doubtful. The patient was 32 years of age and died of rupture of the aorta into the pericardium. The aorta is described as undiseased but thin. The right and left anterior cusps of the aortic valve were united and both showed deposits on them. It is quite possible, if not probable, that in this instance the rupture of the aorta was due to previous inflammatory changes consequent upon disease of the valves, for it has already been seen that the aortic lesion may be so inconspicuous as to be discernible only microscopically. It has also been shown² that a bicuspid condition of the aortic valve renders it peculiarly liable to bacterial invasion.

* *Case* 9, Fig. 21 of previous report.

and these factors together afford a very reasonable explanation of some instances of the above noted association.

The last case of the series to be recorded is particularly interesting because it illustrates in a case of subacute infective endocarditis a stage of relatively acute invasion of the aorta and sinuses with the formation of fissures and minute aneurisms, these forming an important connecting link between the several lesions described.

CASE 17.*

P. C., an electrician, aged 44, was admitted to hospital on the 19th of January, 1922, suffering from subacute infective endocarditis. Having always been healthy he enlisted in 1916, served in France, and was demobilised, feeling perfectly fit, in April, 1919. In October, 1921, he began to complain of shortness of breath and palpitation on exertion, but he continued at work until November, 1921, when his symptoms became worse. A month later his right leg was swollen from knee to ankle.

On admission the patient showed signs of venous stasis with enlargement of the liver and congestion of the lungs. He was thin, and of a muddy complexion, his fingers were slightly clubbed and the spleen was palpable. There was a tender swelling on the back of the right foot and the pulse of the right dorsalis pedis was only just perceptible. The radial pulse was slightly collapsing and the heart moderately enlarged. A to and fro murmur was heard at the aortic cartilage and a rather indistinct diastolic rumble at the apex. The Wassermann reaction was negative. The red blood cells numbered 2,800,000, and the leucocytes 12,700 per c.mm.. A blood culture yielded no growth. The urine contained albumen and blood. With a temperature of between 99 degrees and 100 degrees Fahr. the patient's condition remained about the same until the 22nd of February, when he developed a left hemiplegia and died six days later.

Pathological changes.

Both lungs are congested and edematous with small areas of bronchopneumonic consolidation at the bases. The liver is congested and shows early nutmeg change. The spleen weighs 411 grammes and contains several yellow infarcts. Both kidneys are slightly enlarged, their capsules thickened and their surfaces smooth and mottled. The brain shows areas of softening of the right temporal, frontal, and parietal lobes and of the basal ganglia. About half of the first part of the right middle-cerebral artery is blocked by white clot and the main branches beyond distended with red thrombus. The basal arteries are free from disease. The right posterior tibial artery at about its middle is obliterated and embedded in a mass of fibrous tissue. The heart weighs 468 grammes, both ventricles are hypertrophied and dilated. The pulmonary artery and valves of the right heart are normal. The aortic flap of the mitral valve is very extensively diseased, the vegetations spreading over practically the whole ventricular surface and down the chordae tendinae, many of which are cut across, the ends being covered with vegetations. Vegetations are present on the auricular surface of the posterior flap, extending upwards on to the auricle and downwards on to the chordae tendinae.

There are numerous large vegetations on the aortic valve (Fig. 7), of which commissure A is adherent. The posterior cusp is heavily involved by short vegetations on its ventricular surface continuous below with those on the aortic flap of the mitral valve. They also extend a little way over the margin of the cusps on to its ventricular surface, especially towards the commissures, and have an area of contact along the upper part of the posterior sinus below the ridge. Here there is a small group of minute vegetations in the neighbourhood of each commissure and the remainder of the sinus wall is healthy. At the centres of the margins of both the right and left anterior cusps are long pendulous vegetations (V¹, V²), that on the right anterior cusp having a length

* Previously tabulated as Case 15.

of 2 cm.. The triangle below commissure A is filled up by a large mass of pendulous vegetations. Both the right and left anterior sinuses of Valsalva are free from disease, but on their ridges, and on the aorta above them, are numerous small vegetations. These are most closely grouped above the orifice of the left coronary artery, and in this group of vegetations is seen the stellate aperture (*f*) of an aneurism 2 mms. in diameter; to the left of this is a second aperture (*g*) in the form of an irregular fissure. The remaining vegetations are more scattered, and one of them (*d*) above and a little to the right of commissure A, surmounts a minute stellate break in the aortic wall. The aorta elsewhere is normal except for a few small scattered atheromatous patches. All these aortic lesions lie within the area of contact of the pendulous vegetations attached to the right and left anterior cusps: the tip of the long vegetation on the right anterior cusp when tilted up and swung round reaches even the outlying vegetations. The vegetation marked *e* above commissure C has already been described on page 17, and is shown in Fig. 11. It is an example of an early surface lesion, the further development of which is illustrated by the neighbouring vegetations. In the vegetation marked *h* the appearances are similar except that the vegetation is larger, its centre is necrotic and there is a leucocytic collection in the underlying media. At *i* the vegetation has become crater-like, the superficial elastic laminae are broken while the infiltration beneath is somewhat denser. The adventitia also shows a slight lymphocytic infiltration, and there is some proliferation of its connective tissue. At *k* more of the superficial elastic laminae have been destroyed while the infiltration beneath has increased to the formation of an abscess, which, however, does not open to the surface but is separated from the base of the vegetation by a few remaining laminae. There is a similar though larger abscess at *g*, but here the intervening laminae have given way and it opens on to the surface by the fissured aperture seen to extend across the group of vegetations. This fissure is lined by a fairly thick layer of necrotic material, in which organisms are to be seen and behind which the severed elastic laminae are slightly curved over inwards towards the abscess. At *f* a greater width of the media has given way, resulting in the formation of a small aneurism very similar to that already described in Case 14. But this case not only illustrates the process of advancing infection: in other lesions healing is predominant. The minute protuberance marked *l* is seen to be a small vegetation, the thrombus cap of which has been replaced by young connective tissue consisting chiefly of fibroblasts with a few giant cells. The penetration of the media has advanced to about the same depth as that illustrated in Fig. 11, but in the present instance the connective tissue is, if anything, younger. Similarly with the lesion marked *d*. The minute stellate opening (Fig. 14) is seen to pass entirely through the elastic laminae of the media beneath which it expands into a triangular aneurism lying in the adventitia and which is almost completely filled by recent blood clot (*f.b.c.*). The wall of the cavity (*A.w.*) is completely lined by well nucleated young connective tissue, the cells of which are parallelly arranged.

Numerous very fine elastic fibrils (*e*) are to be seen in this new tissue. On the side of the mouth away from the vegetation this connective tissue lining passes upwards over the ends of broken elastic laminae (*A. m.*) which are here bent over inwards, to become continuous with the intima. At the other side of the mouth the lining tissue merges with the healing base of a vegetation, on the surface of which there are numerous clumps of gram positive cocci (*b. b.*). Through the vegetation itself runs a linear fissure, the margins of which are necrotic and which cuts off from the aortic media a small area of the elastic laminae (*e*) which, as on the opposite side of the mouth, are bent inwards. The media, especially near the base of the vegetation, shows an infiltration of polymorphonuclear leucocytes and lymphocytes lying between the elastic laminae. The adventitia (*Ad.*) is thickened and dense and contains numerous fibroblasts, lymphocytes and plasma cells most densely grouped round the smaller blood vessels. Many of the adventitial vessels, specially those which immediately surround the aneurism, show an advanced degree of obliterative endarteritis.

There is then, in this case, a group of lesions on the aorta such as would be interpreted according to Eppinger and others as being of embolic origin. They are multiple within a circumscribed area: moreover, such a lesion as that described at *g* is usually taken as almost typical of the results of embolism. Yet like the lesions in the other cases of the series they lie within areas of contact of valvular vegetations, and histological examination shows them to be in different stages of development and allows these stages to be traced from one to the other. Further, an extensive examination of the aorta remote from the lesions and of the pulmonary artery does not reveal any deep-seated foci of inflammation to indicate a process of embolism, and this applies also to the aorta and pulmonary arteries of the other cases described in this and the foregoing sections. This is in agreement with McCrae's statement, that in his case a series of sections through the aorta failed to show any localised areas of small celled infiltration in the middle coat which might indicate the earlier stage of infection without aneurism production. It may be concluded, therefore, that the aneurisms arise in a similar manner to the vegetations and the fissures, and that they are to be regarded as a further stage in the development of these lesions.

GENERAL REMARKS.

Putting together the evidence from this series of cases it will be seen the inflammatory lesions of the aorta and sinuses occur only in those cases where the valvular vegetations have possible areas of contact with the aorta and its sinuses, and further that the lesions all lie within these areas. This in itself is sufficient to indicate the casual relationship between surface contact and infection, and is supported by the histological examination of the lesions themselves. It is evident, and has been generally admitted in the past, that the changes seen in an advanced lesion of the aortic wall, such as an

aneurism, can be interpreted as either of embolic or of surface origin. When, however, the developmental stages of these advanced lesions are traced, it is found possible to arrange them in an orderly sequence commencing with minute surface vegetations beneath which the media and adventitia are undisturbed and ending either in a healed sear, a fissure, or in a fully developed aneurism. Also, although those parts of the aorta and sinuses which were superficially free from disease and the wall pulmonary artery have been carefully examined by sections in each case, no deep-seated localised inflammatory changes have been found in a single instance; that is to say, the whole picture presented by the inflammatory lesions of the aorta in the series of cases here presented, is compatible with an infection from the lumen of the aorta and not with an infection arising by way of the vasa vasorum. Although this series does not include any case in which the aortic lesions lay beyond the range of the valvular vegetations, it has already been seen that such do occur, though infrequently. From the evidence given by the present series of cases and from the review of the evidence presented in other reported cases, it would seem that, while embolism of the coronary arteries must be admitted as a possible and rare cause, in the great majority of cases the lesions arise by an infection of the intima from the lumen of the aorta.

Summary of aortic and sinus lesions in 15 cases of subacute infective endocarditis.

Case.	Previously tabulated as Case.	Vegetations.	Fissures.	Aneurisms.
3	19	Many in sinus.		
4	5	A few in sinus.		
5	6	A few in sinus.		
6	11	A few in sinus.		
7	16	Several in sinus.		
8	17	Several round the fissure.	1 in sinus.	
9	20	Several in sinus.	1 in sinus.	
10	10	Several round the fissures.	2 in aorta.	
11	8	One in sinus.	1 in sinus.	
12	12	Many in sinus.	2 in sinuses.	
13	7	Many in sinus.	Several in sinuses.	2 in sinuses.
14	-	Several in aorta and sinuses.		1 in aorta.
15	18	Several in sinus.		1 in sinus.
16	9	A few in sinus.		1 in sinus.
17	15	Many in aorta.	Several in aorta.	2 in aorta.
Total 15		15	7	5

SUMMARY AND CONCLUSIONS.

1. A survey of the present material and of past records shows that an endocarditis associated with lesions of the aortic wall and its sinuses is usually of the subacute infective type.

2. Hitherto these aortic lesions have been interpreted variously as arising either from embolism of the nutrient vessels of the aorta or from infection of the intima.

3. The evidence from previous cases tends to show that although embolism is a possible cause, intimal infection from the lumen of the aorta is the usual mode of origin.

4. Illustrative cases are given in which vegetations on the heart valves have given rise by contact to similar lesions on neighbouring structures.

5. An examination of a series of 30 cases of subacute infective endocarditis reveals lesions of the aorta and sinuses in 15.

6. These lesions are in the form of vegetations, fissures and aneurisms, and their distribution on the surface of the aorta and sinuses leads to the conclusion that they are all due to surface infection from contact with vegetations of the aortic valves.

7. Histological examination confirms this view and shows further that all intermediate stages can be traced from minute surface vegetations, beneath which the aortic wall is undisturbed, up to either a healed scar, a fissure, or a fully developed aneurism.

For Figs. 11 and 14 I wish to express my indebtedness to Sir Thomas Lewis.

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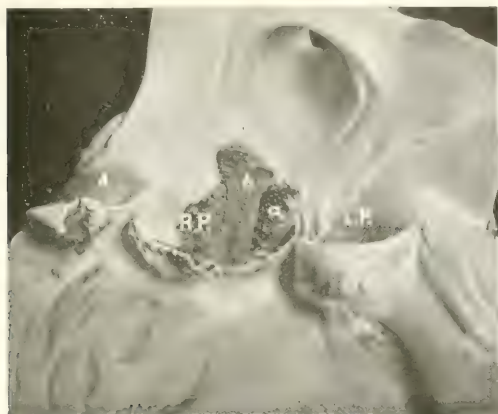


FIG. 1. — *Case 2*. — An approximately natural size photograph of the pulmonary valve, showing the club-shaped vegetation (*a*) and the vegetations on the wall of the pulmonary artery (*b*). The anterior and right and left posterior cusps are marked A, R.P., and L.P., respectively.



FIG. 2. — *Case 3*. — A natural size photograph of the aortic valve. In the usual recording figures the corresponding coronaries are marked A, B and C; the right and left coronary vessels R.C. and L.C., respectively, and the left and right anterior and posterior cusps, L.A., R.A., and P., respectively. V is the septal patch of vegetation, V² and V³ are vegetations on the posterior cusp, and V³ the group of vegetations in the posterior sinus of Valsalva.

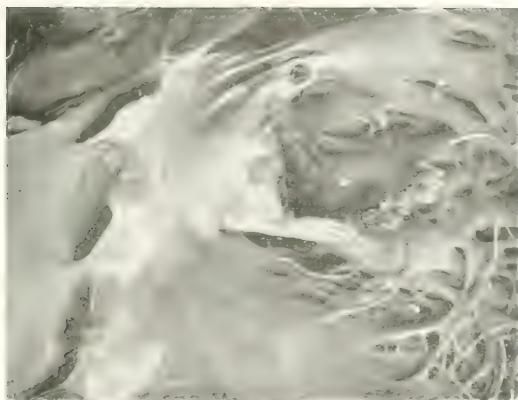


Fig. 1. (Case 1.) A natural size photograph of the mitral valve showing broken chordae tendineae and a mass of vegetation, fungus, *acta*, and the underlying contact of *acta*, *acta*, *acta*, and *acta*.

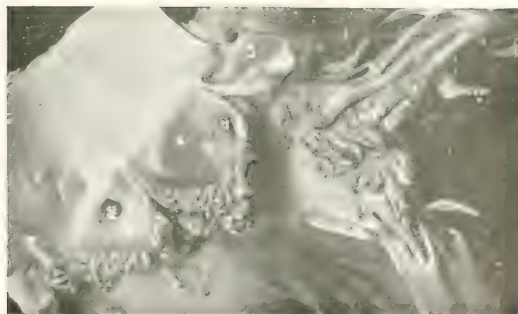


Fig. 2. (Case 1.) A photograph of the aortic valve showing vegetation and *acta* formation of posterior sinus of Valsalva.

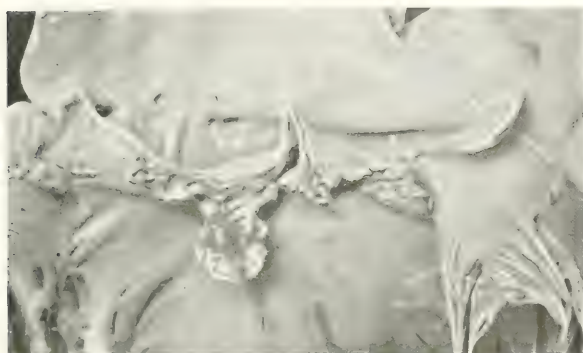


FIG. 5. (Case 10). A photograph of the congenitally bicuspid aortic valve showing the pendulous vegetation attached to the cusps and the fissures in the aortic wall (*f, f*).

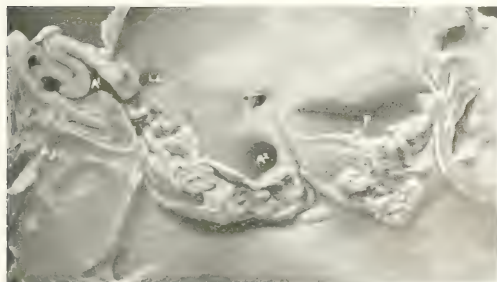


FIG. 6. (Case 13). A photograph, slightly less than natural size, of the bicuspid aortic valve. A' and A'' are aneurisms of the sinus, *f* series of fissures in the sinus wall. The vegetations and tissue in the posterior sinus are not shown.

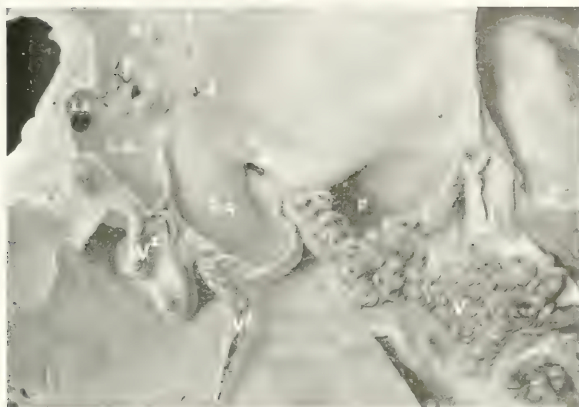


Fig. 7. (Case 17.) A photograph of the aortic valve (0.75). *A*, and *V*, prominent vegetations attached to the cusps; *V'* indicate the various aortic lesions.



Fig. 8. (Case 8.) A photograph (0.5) of the aortic valve (V) with prominent vegetations on the posterior cusp *V*, and the underlying tissue (A) showing endocardial thickening and *n* a small nodule of atheroma.

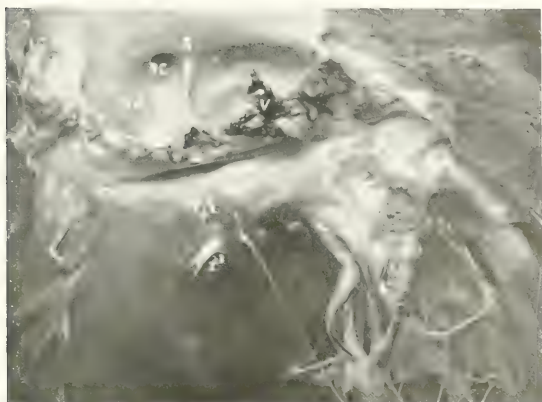


Fig. 9. (Case 7.) A photograph of the aortic valve. *a*–*z* are enumeration of the lesions. *V* is the projecting mass of calcified vegetations on the posterior cusp.

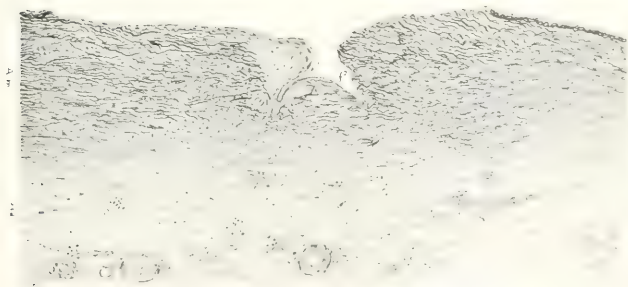


Fig. 10. (Case 13.) Projection drawing of a section (10 microns) of the posterior cusp of the aortic valve. *a*—*z* are points of interest. *a*—*h* are points of interest of a lateral extension. *i*—*z* the main fissure is lined by necrotic debris. *i*—*z* the lateral branch. *z* is unlabeled. The erosion of the intima and media is shown. *Ad.* is the adventitia. *Int.* is the intima. *Med.* is the media. *Ad.* is the adventitia. *Int.* is the intima. *Med.* is the media. *Ad.* is the adventitia.

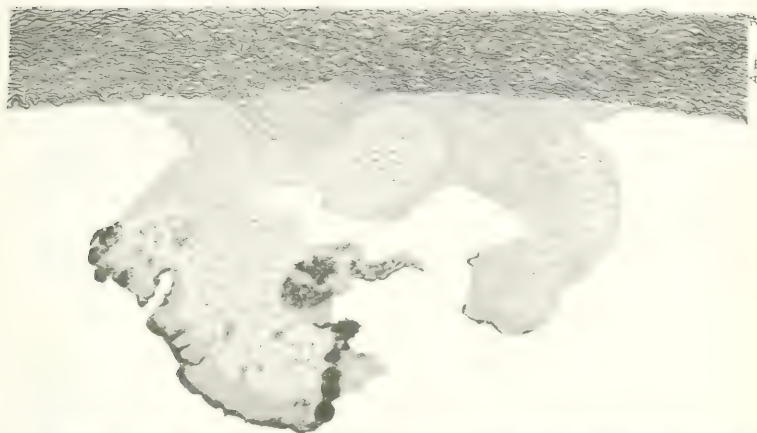


FIG. 11. (Case 17). Projection drawing of a section through the vegetation, marked as in Fig. 7. Nodules, *h*, *h*, *h*, are seen on the surface of the vegetation which is encased in the matrix (Am.), and is being invaded by new connective tissue, which in several places is *h*.

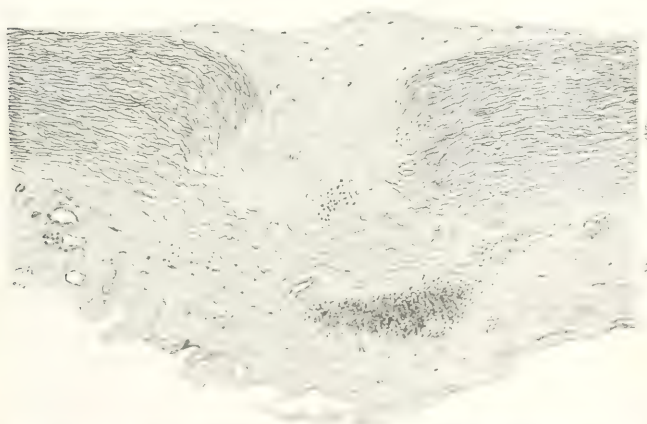


FIG. 12. (Case 13). Projection drawing of a section through the vegetation, marked as in the orthomicro. Am. is the cap with new connective tissue, and *h* is a recent hemorrhage in the thickened adventitia (Ad.). *l* is a collection of fibrin at the base of the scar.

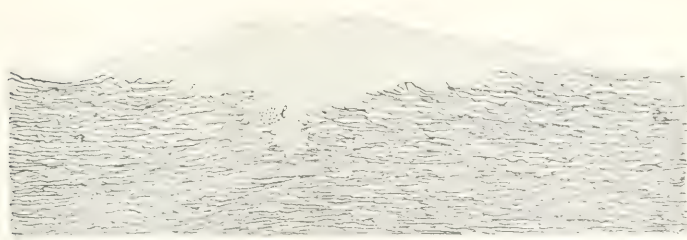


Fig. 13. (Case 16.) Projection drawing of a section (52) through a healed vegetation in the posterior aorta. The break in the aortic media is filled up by connective tissue. *l* = a small lymphocytic collection at the base of the scar.

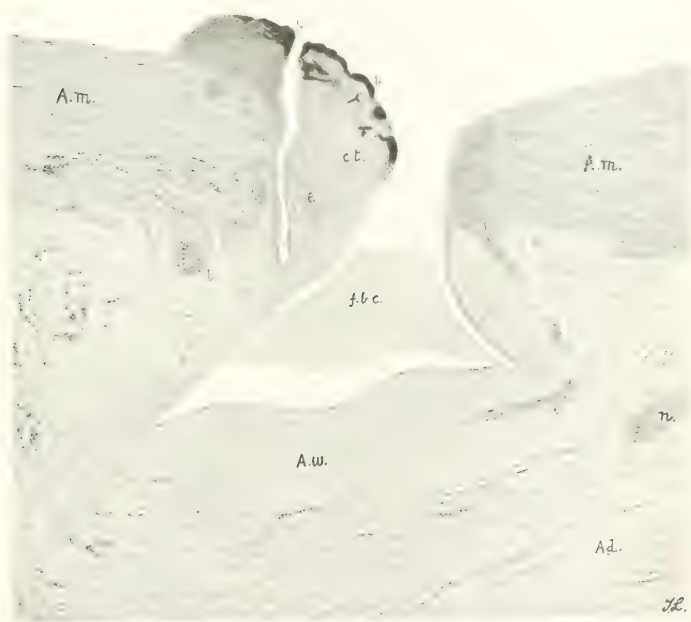


Fig. 14. (Case 17.) Projection drawing of a section (28) through the aortic lesion of a Foet. 7. A.w. = wall of aneurysm. *l* = lymphocytes, *c* = clastic fibres, *n* = nerve, *b* = organisms, *c.t.* = connective tissue. A.m. = aortic media and Ad. the adventitia.

THE REACTION TO EXERCISE OF THE HEART AFFECTED BY AURICULAR FIBRILLATION.*

By HERRMANN BLUMGART, of Boston.

(From the Cardiac Department, University College Hospital Medical
School, London.)

THE following observations were undertaken to determine accurately the reaction of the human heart, affected by auricular fibrillation, to exercise and to compare this reaction with that which is yielded by the heart beating normally.

As is well known, digitalis is capable of controlling the resting ventricular rate in patients who suffer from auricular fibrillation, diminishing an enhanced rate of beating when this is present. A further object of these observations has been to test the control, if any, which digitalis, given in ordinary therapeutic doses, may exert on the rise of ventricular rate produced by exercise in these patients.

OBSERVATIONS.

Comparison of auricular fibrillation and normal rhythm.

By means of the polygraph, the resting heart rates of six normal control subjects of ages similar to the patients, were determined three times at five minute intervals. The subject then stood up, placed one foot on a chair 17 inches in height and lifted himself until standing erect twenty times, repeating the exercise with the other foot. The brachial receiver remained attached to the arm so that when at the cessation of exercise the patient lay down the pulse rate could be determined immediately. Pulse records were taken immediately after exercise, and at subsequent intervals of approximately one minute for six minutes and subsequently at somewhat longer intervals, each period being of about a half-minute's duration. The results of these tests are shown in Table I, the average curve being charted in the dotted curve of Fig. 1.

* Observations undertaken on behalf of the Medical Research Council.

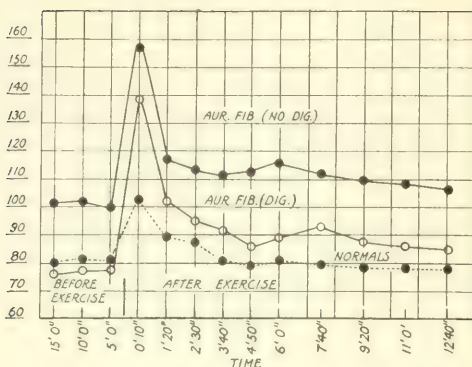


FIG. 1.

TABLE I.

Heart rates of six normal control subjects.

—	Time before exercise.			Time after exercise.									
	15'	10'	5'	0' 10"	1' 20"	2' 30"	3' 40"	4' 50"	6' 00"	7' 40"	9' 20"	11' 00"	12' 40"
Case 1	95	90	90	116	93	89	91	91	91	91	88	90	87
Case 2	82	84	81	102	92	87	89	87	89	88	83	81	86
Case 3	80	83	77	102	90	83	83	82	84	81	81	79	79
Case 4	78	73	73	100	88	79	77	75	81	77	75	77	78
Case 5	73	67	73	100	88	79	73	71	73	74	74	74	76
Case 6	72	78	69	97	82	69	69	69	69	69	73	74	69
Aver. rate	80	79	77	103	89	88	80	79	81	80	79	79	78

A series of nine patients showing auricular fibrillation and little or no cardiac enlargement and no signs of failure was similarly investigated. In order to obtain accurate readings of ventricular rate, electrocardiographic records were used in this series, the curves being taken by means of direct chest leads according to the method described by Drury and Hiescu¹. Exercise was performed with the electrodes strapped in place so that the first records could be taken not later than five to ten seconds after exercise ceased. The results of these tests are shown in Table II, the average curve being charted in Fig. 1 (black circles and continuous line). The conspicuously

TABLE II.

*Heart rates in cases of auricular fibrillation.**Undigitalised.*

—	Time before exercise.			Time after exercise.									
	15'	10'	5'	0' 10"	1' 20"	2' 30"	3' 40"	4' 50"	6' 00"	7' 40"	9' 20"	11' 00"	12' 40"
<i>Case 7</i>	92	86	86	130	107	97	96	98	104				
<i>Case 8</i>	100	109	108	182	129	112	110	117	111	110	112	114	105
<i>Case 9</i>	87	95	95	138	112	91	90	98	104	90	102	93	87
<i>Case 10</i>	84	84	75	135	122	102	96	96	94	98	92	88	86
<i>Case 11</i>	129	115	111	182	149	124	116	117	137	120	124	118	117
<i>Case 12</i>	93	94	94	129	104	96	93	97	90	87	87	90	94
<i>Case 13</i>	115	112	118	165	136	129	124	122	126	128			
<i>Case 14</i>	107	104	104	177	155	143	147	142	140	142	144	142	138
<i>Case 15</i>	112	112	114	144	142	124	131	125	133	133	133	137	132
Aver. rate	102	102	100	156	117	113	111	112	115	113	113	112	109

Digitalised.

—	Time before exercise.			Time after exercise.									
	15'	10'	5'	0' 10"	1' 20"	2' 30"	3' 40"	4' 50"	6' 00"	7' 40"	9' 20"	11' 00"	12' 40"
<i>Case 7</i>	76	76	76	124	96	90	90	90	86	82	84	84	84
<i>Case 8</i>	76	64	68	141	89	79	74	78	73	74	66	76	66
<i>Case 9</i>	68	66	73	130	89	82	76	86	79	80	82	72	77
<i>Case 10</i>	58	64	66	125	90	82	83	68	63	78	74	75	70
<i>Case 11</i>	80	81	82	134	108	102	88	88	86	92	88	81	83
<i>Case 12</i>	86	78	79	135	104	90	80	74	82	78	76	76	77
<i>Case 13</i>	93	96	93	153	118	108	102	105	101	102	105	89	90
<i>Case 14</i>	85	83	81	162	119	111	113	116	110	109	113	108	100
<i>Case 15</i>	96	98	103	152	122	113	112	110	112	114	118	114	108
Aver. rate	79	78	79	139	102	95	91	86	88	93	87	86	84

increased ventricular rate occurring in response to a test exercise in the patients affected by auricular fibrillation sharply contrasts with the relatively small rise observed in the normal subjects. The resting rate in the cases of auricular fibrillation averaged twenty or more beats above that of the normal controls; the rise of rate after exercise was approximately double that exhibited by the normal subjects. This susceptibility of the ventricle in cases of fibrillation of the auricles to respond in an exaggerated fashion is largely responsible for the distress occasioned by exercise in such patients.

It is to be noted that the comparison here instituted is between healthy men who exhibit a normal heart rhythm, and unhealthy men who exhibit fibrillation of the auricles: it is not to be assumed that the patients are normal in respect to anything but the disordered heart mechanism. To obtain a more strictly controlled comparison between the reaction of a

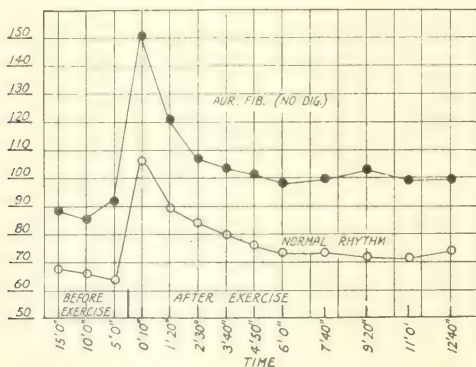


FIG. 2.

heart exhibiting normal rhythm and that affected by fibrillation of the auricles to a standard exercise, a fresh series of patients was tested before and after successful treatment with quinidine sulphate; that is to say, while fibrillation of the auricles and while normal rhythm prevailed. A period of at least twenty-four hours elapsed between the last dose of quinidine and the test. These results are given in Table III, and the average curves are plotted in Fig. 2.

It will be noticed in Fig. 1 that the rate of the normal ventricle falls to normal within four minutes of the end of exercise. In the corresponding group of fibrillation cases, the rate is still elevated at the end of twelve minutes. This difference, however, is not the result of a difference in heart mechanism as the further observations summarised in Fig. 2 clearly indicate.

TABLE III.

*Heart rates in cases of auricular fibrillation.**Before conversion to normal rhythm.*

	Time before exercise.			Time after exercise.									
	15'	10'	5'	0' 10"	1' 20"	2' 30"	3' 40"	4' 50"	6' 00"	7' 40"	9' 20"	11' 00"	12' 40"
<i>Case 16</i>	111	102	108	176	127	120	119	111	110	112	119	118	110
<i>Case 17</i>	61	64	65	114	92	79	71	74	71	76	73	70	72
<i>Case 18</i>	81	76	73	152	116	98	96	92	93	87	90	89	90
<i>Case 19</i>	89	87	91	132	116	111	108	101	97				
<i>Case 20</i>	99	100	118	198	148	120	122	121	119	120	118	121	122
Aver. rate	88	86	91	150	120	106	103	100	98	99	102	99	99

After conversion.

	Time before exercise.			Time after exercise.									
	15'	10'	5'	0' 10"	1' 20"	2' 30"	3' 40"	4' 50"	6' 00"	7' 40"	9' 20"	11' 00"	12' 40"
<i>Case 16</i>	84	78	77	116	98	95	90	88	85	87	85	93	88
<i>Case 17</i>	54	52	53	91	73	70	60	59	60	58	62	61	58
<i>Case 18</i>	68	68	60	98	70	79	80	70	68	67	66	62	68
<i>Case 19</i>	74	74	69	104	86	80	86	82	83	81	79	81	73
<i>Case 20</i>	56	58	58	122	114	96	78	80	76	70	68	68	68
Aver. rate	67	66	63	107	88	84	79	76	74	73	72	73	71

When the same series of patients is investigated in the stage of fibrillation and again while normal rhythm is present, the rate at which the ventricular rates decline is found in both instances to be much the same: in both the return to the previous rate is greatly delayed. The delayed return in fibrillation of the auricles is not due, therefore, to the abnormal mechanism but to some additional factor existing in these patients.

It is also seen that the striking contrast between the rise of ventricular rate of the normally beating heart of healthy subjects and of the ventricle in auricular fibrillation (Fig. 1) is displayed to a much smaller extent when the normally beating hearts of the same patients are used as controls (Fig. 2). In both series the reaction is similar when the auricles are fibrillating, but

when in patients who exhibit fibrillation the normal rhythm is restored, acceleration of the ventricle in response to exercise is still abnormal in its degree.

In the two respects, namely, in the exaggerated rise of rate, and in the undue prolongation of the raised rate, the reaction of the heart, whose mechanism has been converted from fibrillation to normal, resembles that seen in many conditions of ill-health and notably in the symptomatic condition described as the "effort syndrome."

TABLE IV.

Auricular and ventricular rates before and after exercise in auricular fibrillation.

	Rate before exercise.		Rate after exercise.		Difference.	
	Auricle.	Ventricle.	Auricle.	Ventricle.	Auricle.	Ventricle.
Case 21*	504	70	464	89	- 40	+ 19
Case 22*	455	75	416	94	- 39	+ 19
Case 23	444	85	386	130	- 58	+ 45
Case 24	500	80	436	134	- 64	+ 54
Case 25*	470	77	458	130	- 12	+ 53
Case 26*	453	87	443	122	- 10	+ 35
Case 27	575	100	518	151	- 57	+ 51
Case 28	526	75	511	103	- 15	+ 28
Case 29	435	75	407	127	- 26	+ 52
Case 30	473	70	434	97	- 39	+ 27
Case 31	425	63	410	122	- 15	+ 59
Case 32	455	65	470	93	+ 15	+ 28
Case 33	422	83	429	119	+ 7	+ 36
Case 34	428	58	463	67	+ 35	+ 9
Average	470	75	446	113	- 23	+ 39

* These patients were on ordinary therapeutic doses of digitalis.

Effect of exercise on rate of auricular oscillations. I am indebted to Dr. C. C. Hiescu for the following observations upon a series of cases of fibrillation of the auricle, in which he tested the effects of exercise upon the rate of the auricular oscillations, in patients chosen for this purpose. The method of recording was similar to that here described, but the lead was specially arranged to render the auricular oscillations prominent; the test exercise employed was the same as here described. The results are summed

up in Table IV, in which it will be seen that with few exceptions the rate of the auricular oscillations declines on exercise, while the ventricular rate rises. This reaction to exercise, though not quite invariable, conforms to the general rule, that in auricular fibrillation the changes in rate are in opposite directions in auricle and ventricle² and ³.

Comparison of auricular fibrillation cases before and after digitalis therapy.

The first series of patients, the series from which Fig. 1 is compiled, came under continuous treatment with digitalis for a period of a month, ten minims of the tincture of digitalis being given thrice daily. At the end of this period they were again tested in exactly the same fashion to determine to what extent digitalis controlled the resting rate and particularly the rise of ventricular rate on exercise. The results of these tests are shown in Table II, the average curve being charted in Fig. 1 (white circles).

It will be seen that, as is usual, the resting rates of ventricle are materially lower, while digitalis is being administered in ordinary therapeutic doses. Although there is this control of the resting rate and although the highest rate, reached by the ventricle in response to a fixed exercise test, is lower than in the undigitalised subject, yet the rise itself, counted as so many beats per minute, is actually somewhat greater under digitalis than when this drug is not administered. In other words, the reaction of the ventricle to exercise, when the auricles are fibrillating, is not subdued by digitalis; on the contrary, it is if anything exaggerated. The larger rise of rate on exercise may possibly be interpreted legitimately, if it is imagined that the exercise reaction remains unchanged in extent, while exercise tends at the same time to abolish the control which digitalis exerts on the resting rate.

CONCLUSIONS.

1. As compared to the reaction of a normal heart, the heart affected by auricular fibrillation responds to test exercise by a disproportionate rise in ventricular rate, and a delayed return to the previous resting level.

2. The delayed return of the ventricular rate in auricular fibrillation to the previous resting level is not due to the abnormal mechanism, but to an additional factor. For it is also exhibited, as is also an exaggerated rise of ventricular rate in response to exercise, by the same patients when the heart's mechanism has been restored to normal. In these respects the reaction is similar to that found in the "effort syndrome."

3. Digitalis in ordinary therapeutic doses fails to protect the ventricles from the exaggerated response to exercise.

4. In auricular fibrillation, when the ventricular rate rises as a result of exercise, the auricular rate generally falls.

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CLINICAL "CAPILLARY PULSATION."

By ERNST P. BOAS.

(*From the Medical Division, Montefiore Hospital for Chronic Diseases,
New York.*)

IN a recent paper Sumbal⁸ has reported his study by a microcapillary method of the phenomenon of clinical "capillary pulsation" and has come to the conclusion that clinical capillary pulsation of the lip, as seen in cases of free aortic regurgitation, is a phenomenon of the capillaries themselves. In my original observations¹ the capillaries of the skin overlying the nail bed were studied. Due to the method employed the visualisation of the capillaries was rendered difficult by the movements of the fingers that accompany each pulse beat. In the light of Sumbal's observations, I have reinvestigated the subject, employing a different method.

Müller's Hautkapillarmikroskop⁴, manufactured by Zeiss, was employed in these studies. In this instrument the ordinary tube of a microscope is fitted, by means of a micrometer screw which is used for focussing, into another tube, having a flat base with a central circular opening through which the skin is observed. A small electric light bulb is inserted in the second tube near its base. The magnification is 60 diameters.

The apparatus is placed on the skin and the capillaries may be observed directly. The movement of the capillaries out of the focal plane with each pulse beat is avoided by the use of this instrument, and the skin of every part of the body is readily accessible to observation.

Eight patients with aortic insufficiency, presenting clinical "capillary pulsation," were examined. In each patient the capillaries were studied on the inner and outer aspect of the lip, on the finger over the root of the nail, and on the forehead after the skin had been rubbed to provoke reddening and systolic flushing of the skin. A glass slide was interposed between the skin and the microscope, so that uniform pressure could be exerted on the underlying structures. On the cutaneous surfaces castor oil was used to render the capillaries visible. On the mucous surface of the lip it was unnecessary to employ oil.

The microscope was manipulated so that varying degrees of pressure from the lightest, just corresponding to the weight of the glass slide, to the heaviest, which accomplished complete blanching of the microscopic field, were employed. In every case the behaviour of the capillaries was noted in

particular during the time when a definite paling and flushing of the whole microscopic field was evident.

In two of the patients examined definite pulsation of the capillaries of the lip was observed. In four patients, although there was a very distinct paling and reddening of the whole field, there was no visible pulsation in the capillaries of the lip, except in occasional isolated vessels, and in them it was not very marked. A rhythmic expansion of the end of the capillary loop was seen only rarely. At certain pressures the flow in some of the capillaries was pulsatile and synchronous with the heart beat. Such an intermittent flow, however, occurs at certain degrees of skin pressure in patients who have no clinical "capillary pulse." The important point which I wish to emphasise is that in these cases, although the rhythmic paling and flushing of the microscopic field was very evident, only very few of the capillaries in that same field exhibited evidences of pulsation, or intermittency in blood flow. In most of the capillary vessels the streaming was rapid and uninterrupted. In some the flow was halting or even arrested. At no time, not even in the cases showing definite pulsation of the capillaries, was a rhythmic emptying and filling of the capillaries seen. In two patients there was no evidence whatsoever of capillary pulsation of the lip.

The skin of the forehead was reddened by preliminary friction, and in all cases exhibited definite flushing and paling. Yet on microscopic examination, although the background of the microscopic field showed the rhythmic change of colour very clearly, very few capillaries were visible and these did not pulsate. The skin of the forehead, as has been pointed out by Niekau⁵ is thickly studded with sebaceous glands and there are few visible capillaries. In one patient who was sun-burned many capillaries were visible on the forehead, and clinical "capillary pulsation" was particularly well marked, yet even in him there was no evidence of pulsation of the capillaries themselves.

In the examination of the finger care was again taken to study the capillaries while the background was flushing and paling. Sumbal's criticism of my previous observations on the grounds that the skin overlapping the nail bed is of relative horny consistence, and that clinical "capillary pulsation" is not seen to occur in it is inapplicable because in my present, as well as in my previous, studies I did not report on the capillaries in that portion of the skin which is growing over the nail, as the cuticle. The capillaries immediately behind this zone were observed, and in this area clinical "capillary pulsation" does occur. Yet in none of the present series of cases was a microscopic pulsation of the capillaries seen in this region. Here, as in the lip, the blood flow in the capillaries varied from a rapid streaming to complete stagnation.

Two observers, Secher⁶ and Fischl², have reported independently that they have been unable to observe a true capillary pulse in patients who

exhibit clinical "capillary pulsation." In a few cases Secher did observe pulsation in some capillaries, but he concludes that clinical "capillary pulsation" is conditioned by the varying degree of filling of vessels larger than capillaries. Years ago Herz³ expressed the opinion, based on indirect evidence, that the clinical "capillary pulse" is really an arteriolar pulse.

It seems clear that Sumbal is correct in his observation that actual pulsation of the capillaries occurs in patients with free aortic regurgitation; but his deduction that clinical capillary pulsation of the lip is a phenomenon of the capillaries themselves is open to question. The fact that in the presence of clinical "capillary pulsation" of the lip, forehead and finger there may be no visible pulsation of the capillaries, or pulsation in only a few capillaries, speaks against his conclusion. According to Spalteholz⁷, the blood supply of the cutis consists of the capillary loops in the papillæ of the skin, and two layers of subpapillary arterial and venous plexuses. It is only in the papillæ that the arterioles of the skin become true capillaries, although the vessels of the subpapillary plexus have almost the same structure as have capillaries. It has been noted by many observers that when pressure is applied to the skin while it is studied through a microscope, paling takes place without any change in the degree of filling of the visible capillaries. As a matter of fact it is difficult in most cases to empty the capillaries of their blood. Yet the skin may pale following the application of a pressure of a few millimetres of mercury.

These observations, as well as the fact noted by Weiss, that the degree of redness of the normal skin is determined not by the number of visible capillaries but by the distribution of the subpapillary plexuses, show that the normal skin colour, as well as changes in skin colour, are determined not so much by the degree of capillary filling, but in large part by the degree of filling of the subpapillary arterioles and venules. Moreover, if the capillary pulse were a phenomenon of the capillaries themselves one would expect to find a rhythmic emptying and filling of the capillaries, accompanying the marked paling and flushing that is so often observed. This I have never seen, and Sumbal reports that he has noted it only as an occasional occurrence in isolated capillaries. It is difficult to see how an expansile pulsation or regular acceleration of the blood stream can determine a marked variation in colour of the skin.

In spite of the fact that actual pulsation of capillaries may be demonstrated in some patients with aortic insufficiency, the phenomenon is not sufficiently constant or intense to explain the clinical "capillary pulse." The subpapillary arterial and venous plexuses are the chief determinants of the colour of the skin. Ordinarily the component vessels of these plexuses cannot be clearly distinguished microscopically, so it is impossible to ascertain by direct observation if the venules share with the arterioles in the production of the clinical capillary pulse. In a measure, the distinction between the

capillary loops of the papillæ and the subpapillary plexus is a matter of definition, for except for a difference in size they resemble one another closely in structure.

We are thus warranted in concluding that the clinical "capillary pulse" on the lip, forehead, and on the finger over the root of the nail is mainly a phenomenon not of the capillaries of the papillæ of the skin or mucous membrane, but of the subpapillary and cutaneous vascular plexuses.

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REPORT OF A CASE OF AURICULAR FLUTTER IN WHICH
VAGUS STIMULATION WAS FOLLOWED BY AN INCREASE
IN THE RATE OF THE CIRCUS RHYTHM.

By FRANK N. WILSON.

(From the Department of Internal Medicine, University of Michigan Medical
School, Ann Arbor.)

THE effects of vagal stimulation upon the rhythm of the auricles in experimental auricular flutter have been examined in detail by Lewis, Drury and Bulger.² Of the effects observed by them one of the most frequent was a gradual acceleration of the auricular rate. This effect usually followed relatively light vagus stimulation, and attempts were subsequently made to produce it in clinical flutter by pressure upon the vagus in the neck.³ These attempts were unsuccessful and an examination of published curves showing the effects of this experiment upon flutter in man failed to disclose any instance in which the auricular rate had been materially modified. The case of auricular flutter described below in which ocular pressure caused a conspicuous acceleration of the auricles appears, therefore, to stand by itself.

The patient, a university student aged 20, complained of rapid and irregular heart action which came on suddenly about one hour after he had taken part in the excitement and strenuous exertion of an undergraduate contest. He had had a similar attack two years before while engaged in playing basket-ball. At the time of the examination, which was made on the next day but one following the onset of the disorder, the heart was beating irregularly at a rate of about 140 per minute. There was no definite

* Levine and Frothingham¹ have described a case of auricular flutter in which deep breathing produced slight changes in the auricular rate.

evidence of cardiac enlargement. An indistinct rumbling diastolic murmur was heard at the apex and a diagnosis of mitral stenosis was made; this diagnosis was confirmed after the cessation of the abnormal rhythm, when the murmur became plainly audible.

Electrocardiographic observations. The electrocardiogram showed auricular flutter with an auricular rate of about 380 per minute. The ventricles were responding irregularly to every third or fourth circus contraction. The flutter complex was 8 to 9 mm. in amplitude (8 to 9 $\times 10^{-4}$ volts) in leads *II* and *III* and about 1 mm. in amplitude in lead *I*. (Chest leads were also made. In the anterior-posterior lead* the flutter complex was isoelectric: in a lead parallel to the right border of the sternum it measured 10 mm.; and in a lead from the second right intercostal space to a corresponding point on the left side its amplitude was 1 mm..

The inhalation of amyl nitrite produced a conspicuous increase in the ventricular rate and a slight fall in the auricular rate. The control curve taken immediately before the drug was given shows an auricular rate of 354 with 4 to 1 ventricular response. After amyl nitrite the auricular rate was 342 and the ventricles responded to every second circus contraction.

Three attempts were made to stimulate the vagus by pressure upon the eyeball. The first produced ventricular standstill for about three seconds; the auricular rate was not appreciably changed. In the other two observations, in which a ventricular standstill of about six seconds resulted, there was a conspicuous change in the flutter rate. One of the curves has been carefully measured with the Lucas comparator and is shown in Fig. 1. The other curve is very similar, but could not be measured because of the failure of the time marker. The first seven cycles of Fig. 1 average 0.163 of a second in length. The maximal variation in cycle length is about 0.01 of a second, and there is a tendency for long and short cycles to alternate, which becomes more conspicuous in cycles 8 to 11. The increased variation of these last cycles is accompanied by variations in the form of the flutter complex. With cycle 12 there is a sudden decrease in cycle length and from this point onward the variations of the interval are slight if cycle 23, the measurement of which is somewhat interfered with by one of the time lines, be disregarded. The average length of cycles 12 to 39 inclusive is 0.1309 of a second.

The administration of quinidin sulphate was followed by a progressive decrease in the flutter rate ending in return of the normal rhythm. The details are given below in tabular form.

* The Z-electrode was placed over the second right costal cartilage, the C-electrode in the right interscapular region. The distance between the electrodes was 8 inches. In the second chest lead mentioned the Z-electrode was placed upon the second right costal cartilage and the C-electrode 6 inches below this point. In the third chest lead the Z-electrode was placed in the second right intercostal space 3 inches to the right of the midline and the C-electrode in the second left intercostal space 3 inches to the left of the midline.

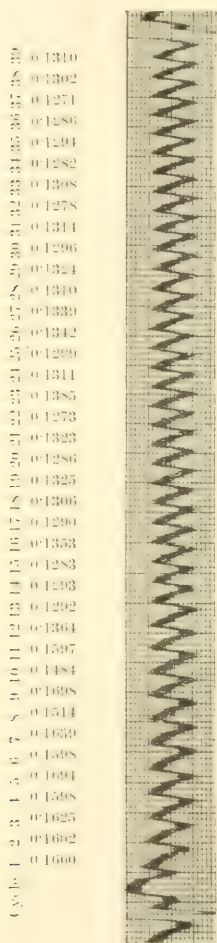


FIG. 1. Chest lead parallel to right sternal border. 1 mm. = 1 $\times 10^{-5}$ volts. Time in fifths and twenty-fifths of a second. Effect of vagus stimulation on the auricular rate.

Curve.	Time.	Auricular rate.	Ventricular response.
467 (control)	2.50 p.m.	373	Irregular.
12 grains quinidin sulphate given at 2.50 p.m.			
468	3.20 p.m.	344	Irregular.
	3.26 p.m.	346	..
	3.33 p.m.	342	..
469	4.27 p.m.	333	..
6 grains of quinidin sulphate given at 4.30 p.m.			
470	4.54 p.m.	300	2 to 1
	5.20 p.m.	275	2 to 1
	8.29 p.m.	Normal rhythm.	

Discussion.

For the gradual increase in the auricular rate produced by vagus stimulation in experimental auricular flutter, Lewis and his collaborators² offer two possible explanations:—

Explanation 1. It has been shown that in many instances of experimental flutter the speed with which the excitation wave travels is greatly reduced and may not exceed one-half the speed found when the normal rhythm prevails. This subnormal rate of conduction has been found to depend upon the partially refractory condition of the muscle through which the crest of the excitation wave is advancing. Islands of refractory tissue encountered by the wave force it to pursue a sinuous course and consequently greatly retard its progress. Vagus stimulation, by shortening the refractory period of the auricular muscle, tends to reduce the number and the size of these islands of refractory tissue or to abolish them altogether; and, therefore, to render the path of the circulating excitation wave less sinuous and consequently shorter, and to increase the rate of the circus rhythm.

Explanation 2. The second explanation is offered to account for those instances in which the speed of the excitation wave is not initially reduced, but in which, nevertheless, vagus stimulation increases the flutter rate. Let us assume that the excitation wave is pursuing a path which does not closely encircle a natural orifice. Interior to the path pursued many shorter paths will then exist which are not open to the circus wave because of the length of the refractory period. For it is obvious that a circus contraction can only be set up in a ring of muscle when the time taken by the

excitation wave to travel completely around the circumference of the ring is less than the absolute refractory period. Vagus stimulation increases the flutter rate by shortening the absolute refractory period and thus permitting the circus wave to accept a shorter path.

Both of these explanations are similar in principle in that they attribute the increase of the flutter rate produced by vagus stimulation to a shortening of the path of the circus wave dependent upon a decrease in the length of the refractory period.

To decide which of these two explanations should be adopted in accounting for the acceleration of the auricular rate produced in our patient by vagus stimulation is a task which should not, perhaps, be attempted. Nevertheless, the intervals of Fig. 1 show certain peculiarities which afford a clue of the underlying mechanism.

The tendency to alternation shown by the first seven intervals of Fig. 1 suggests that the excitation wave was advancing in partially refractory tissue and, therefore, that the speed of conduction was reduced. To this view, however, the unusually high auricular rate, the increased alternation of cycles 8 to 11, and the sudden change in auricular rate at cycle 12, so it seems to us, are opposed. The high auricular rate indicates a high conduction rate or an unusually short path. More conspicuous alternation suggests that the circus wave is advancing in partially refractory tissue of greater density; that the barriers of refractory tissue encountered are larger or more numerous. But such larger or more numerous barriers would demand a decrease in the rate of conduction which is not consistent with an increase of the flutter rate unless the path of the circus wave is simultaneously shortened. The principles of *Explanation 1* demand that a sudden increase of the auricular rate be attributed to an abrupt decrease in the length of the refractory period. The increased auricular rate produced in experimental flutter by vagus stimulation, however, occurs after a long latent period which suggests that the metabolic or physico-chemical changes induced by vagus stimulation upon which it depends develop slowly. It seems unlikely, therefore, that vagus stimulation can produce sudden changes in the refractory period; but if such changes can occur they should occur at the beginning of vagus stimulation. The sudden change in auricular rate shown in Fig. 1 did not occur at the beginning of vagus stimulation, but some seconds later: it cannot logically be attributed to a sudden reduction of the refractory period.

It seems probable, therefore, that the acceleration of the auricular rate produced in our patient by vagus stimulation was due to a change in the path of the circus wave. We may suppose that in spite of the slight tendency to alternation shown by the early cycles of Fig. 1 the rate of conduction was nearly normal and that the gradual reduction of the refractory period brought about by vagus stimulation had at first no effect upon the auricular rate. Eventually, however, the refractory period became so short that a

new path, much shorter than the old one, was opened to the circulating wave. We must assume also that no path of intermediate length existed. At first this new path appears to have been accepted on alternate revolutions (cycles 8 and 10), but a further reduction of the refractory period enabled the circus wave to follow it continuously. We may account for the greater length of cycles 8 and 10 as compared with cycle 12 and those which follow it by supposing that when the circus wave first took up the new path it met with large barriers of refractory tissue which disappeared under the continued influence of vagus stimulation.

The variations in the intervals of Fig. 1 from cycle 8 to cycle 11, inclusive, are accompanied by variations in the form of the flutter complex. The downstroke corresponding to interval 9 closely resembles the downstroke corresponding to interval 11; both are conspicuously notched. The complexes corresponding to intervals 8 and 10 show a somewhat less striking similarity of form. These variations in the form of the flutter complex are consistent with the interpretation of Fig. 1 given above.

The fall in auricular rate produced by amyl nitrite though slight is in the expected direction, and may have been due to an increase in the length of the refractory period brought about by a decrease of vagal tone. We should attach greater importance to it were it not that the control curve taken immediately before the amyl nitrite was given shows an auricular rate (354) considerably below that shown by all other control curves (375 to 380). For the peculiarity of this control curve we have no explanation.

SUMMARY.

A case of auricular flutter is reported in which vagus stimulation was followed by a conspicuous increase in the rate of the circus rhythm.

The increase in auricular rate is attributed to a shortening of the path of the circus wave brought about by a reduction in the length of the refractory period of the auricular muscle.

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VENTRICULAR TACHYCARDIA DURING AN ATTACK OF PAROXYSMAL AURICULAR TACHYCARDIA.

By PAUL S. BARKER (St. Louis).

*(From the Department of Internal Medicine, Washington University School
of Medicine.)*

VENTRICULAR tachycardia is a comparatively rare disturbance of the cardiac mechanism. About twenty undoubted cases have been recorded and the condition has been fully described^{2,3}. Recently Strong and Levine⁴ have pointed out that in paroxysms of ventricular origin the ventricle is often irregular, as opposed to the usual regularity of the heart in paroxysms of auricular origin. The case here reported is one of auricular tachycardia, briefly disturbed by an irregular tachycardia of ventricular origin. The only case recorded at all resembling this is Hoffmann's¹. In this a paroxysm of auricular tachycardia terminated in a paroxysm, subsequently regarded² to be a ventricular tachycardia, but so irregular that it was thought at the time to be ventricular fibrillation. The irregularities described by Strong and Levine were of much slighter degree; nevertheless, the different forms may have much in common.

A housewife, aged 47, was admitted to hospital on April the 16th, 1923, complaining of nervousness and attacks of palpitation. The history of past illnesses contains little that is relevant to her main condition. Her attacks of palpitation began at the age of 11. They have occurred irregularly and as often as four times in a week. They lasted from one to two hours until four years ago, when they became of many hours' duration. They are abrupt in onset, and offset, and are of sufficient severity to cause great anxiety. There is no pain, but if an attack is long continued the left arm and chest feel weak. For years moderate dyspnoea on exertion, anorexia, and constipation have been experienced, but no syncope or œdema.

The woman is thin; but a complete clinical examination reveals nothing abnormal in the heart or remaining organs, with the exception of a retroverted uterus. A normal electrocardiogram of April the 17th is shown in Fig. 1.

At noon on April the 23rd the patient was found in an attack of tachycardia. The heart beat between 200 and 240 per minute, the pupils were dilated, and there were hyperpnœa, flushing of the face, and extreme anxiety. The attack terminated in a few hours. Electrocardiograms taken during the attack showed auricular tachycardia, with a short period of irregular ventricular tachycardia interpolated in lead *I* (Fig. 2). The complexes of the latter are abnormal, of the type of ventricular extrasystoles, and irregular in form and time relations; the rate is 267 per minute. The impulses appear to spring from at least two, if not more, ventricular foci. No auricular complexes can be identified in any part of these curves.

SUMMARY.

A case is presented showing a short run of irregular ventricular tachycardia during an attack of paroxysmal auricular tachycardia.

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FIG. 1. April 17th, 1923. Normal mechanism, in leads *I*, *II* and *III*. Time in 0.2 of a second, 1 cm. = 1 millivolt.

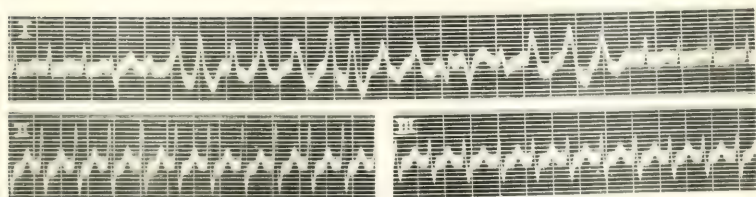


FIG. 2. April 23rd, 1923. Paroxysmal auricular tachycardia with a period of irregular ventricular tachycardia in lead *I*. Time in 0.2 of a second, 1 cm. = 1 millivolt.

OBSERVATIONS RELATING TO THE NERVE SUPPLY OF THE CORONARY ARTERY OF THE TORTOISE.*

PART I. DIRECT OBSERVATIONS OF THE ARTERY.

By A. N. DRURY and FRED. M. SMITH (Chicago).

(From the Cardiac Department, University College Hospital Medical School.)

Historical.

THE question as to whether the coronary arteries are provided with a vasomotor mechanism through the vagi and sympathetic nerves has been extensively investigated. There is, in fact, at the present time no consensus of opinion as to whether such a vasomotor mechanism exists, so varied have been the results of stimulating these nerves.

Adrenalin on isolated arteries. The question has been approached through the study of the action of adrenalin on short sections of coronary artery suspended in Ringer's^{2,7,9-10-14,18} solution. By this method adrenalin has repeatedly been found to produce a dilatation of coronary artery strips from the sheep, goat, ox, calf and rabbit. Barbour², however, who used human coronary arteries removed at autopsy while the body was still warm, observed a constriction; but in a similar series of experiments he noted dilatation when the coronary arteries of the calf, sheep, and pig were used. Wiggers²⁴ has justly pointed out that the above method investigates only the larger arteries, and does not take into consideration the remaining portion of the coronary arterial system. Cow⁷ noted that strips taken from different sections of the same artery varied in their response to adrenalin. In the recent work on capillaries much additional information has been furnished by Krogh^{11, 12, 13} concerning the irregular action of adrenalin on arteries. He states that in the brown frog numerous arteries of the tongue are strongly constricted by adrenalin, while others, especially the larger arteries, are unaffected. Furthermore, he has pointed out that the superficial arteries of the skin and web of the frog may react differently to adrenalin

* Observations undertaken on behalf of the Medical Research Council.

in different sections of their course. If a drop of 0.1 per cent. adrenalin is placed on an artery there may be no perceptible change in size. If, however, drops are now placed at short distances apart along the course of the vessel at intervals of half a minute or more, a region of the vessel is at last reached which responds; on repeating the experiment the same section of the vessel constricts again. Thus the observations on the action of adrenalin on pieces of coronary arteries seem to show a variation in reaction in different animals.

Observations on coronary flow. It has frequently been observed that adrenalin increases the rate of coronary flow both in the intact heart^{15,16,17,23} and in the perfused heart^{2,4,21,23}. Brodie and Cullis⁵, employing the latter method, noted a decreased flow with small doses of adrenalin; but with doses of sufficient strength to accelerate the cardiac rate, the coronary flow was augmented. Barbour and Prince³ observed a decreased coronary flow in the perfused heart of the monkey, whereas in rabbits employed in a similar series of experiments the flow was constantly increased. Wiggers²³ and Rabe²⁰ invariably found that the flow through the coronary vessels diminished when adrenalin was perfused through the quiescent heart.

It is an extremely difficult matter to maintain all the factors which influence coronary artery flow constant in the intact heart before and after the administration of adrenalin. The heart lung preparation of Markwalder and Starling⁷ comes nearest, perhaps, to meeting such requirements. Wiggers²¹, however, has pointed out that the increase in the coronary flow observed by these investigators may, perhaps, be explained on a mechanical basis from an increase in rate and amplitude of cardiac contraction. The same objections may be raised concerning the perfused heart unless the heart is quiescent, as in the observations of Wiggers²³ and Rabe²⁰. Moreover, as Wiggers²³ has pointed out, errors arise in perfusing a heart from the aorta as leakage at the aortic valves is almost certain. Furthermore, he establishes by a preliminary investigation that an increase or decrease in the outflow from the right heart cannot be interpreted as being due to changes in the coronary vessels unless it can be shown that the pressure of the perfusing solution supplying the coronary arteries remains constant, that the size of the chambers, which exist as an intermediate reservoir between the heart veins and the registering apparatus, and the massaging effect of the heart muscle on the intermural vessels remains the same. These are all factors which may influence the apparent outflow from the coronary veins. This method of investigating the action of adrenalin on the vessels has again led to an apparent conflict of evidence, probably due to the variation in the direct and indirect action which adrenalin may exert.

The results of stimulating the sympathetic and vagus nerves has varied in the hands of different investigators. Morowitz and Zahn¹⁷ observed an increased coronary flow, as determined by measuring the outflow from a cannula inserted into the coronary sinus, during sympathetic stimulation. In these experiments neither the cardiac rate nor the blood pressure was

controlled, and the augmented coronary flow could well be attributed to these mechanical factors. Wiggers²³ reports a decreased flow from a wounded coronary vein during the stimulation of the vago sympathetic nerves of the dog after atropinisation: as, however, the cardiac rate and blood pressure remained constant, the evidence for vagal stimulation is not quite clear. More recently Sassa²² has studied the coronary flow by cannalising the coronary arteries, as suggested by Porter²⁰, in the intact and isolated heart of the cat, and has measured the rate of inflow by Atzler and Frank's method¹ which removes some of the objections put forward by Wiggers. A decreased flow was usually recorded in the beginning of sympathetic stimulation even with an increased cardiac rate, whereas on vagal stimulation there was an initial increase in the rate of inflow associated with a reduced cardiac rate. He was apparently uncertain as to the interpretation of these results, and refrains from attributing the action directly to the cardiac nerves. It was unfortunate that this worker did not control the cardiac rate; his results are very suggestive, but might have been more striking had he taken this factor into consideration.

Direct inspection of vessels. Finally the action of the vagi and sympathetic nerves on the coronary vessels has been studied by inspection with the naked eye or with the aid of a magnifying glass. Dogiel and Archangelsky² observed the change in the size of the coronary vessels of the cat, dog and tortoise after bringing the heart to a standstill by vagal stimulation and then stimulating the sympathetic nerve. They obtained the sympathetic effect in the cat and dog by stimulating the annulus Vieussensii, and state that they repeatedly noted a decrease in the size of the superficial coronary arteries with an increase in the diameter of the accompanying veins during sympathetic stimulation. They published photographs of the heart of the dog and tortoise during the period of standstill before and after stimulation of the sympathetic, but these photographs do not clearly show the results which they wish to illustrate.

Observations.

The following report is based on observations on the action of adrenalin and vagal stimulation on the coronary arteries of the tortoise (*Testudo graeca*). The tortoise has been chosen because it has a heart which beats slowly and without much movement, because the exposed heart remains in good condition for hours at room temperature, and because it is believed that the vagus has no action on the force of the contraction of the ventricle. The animal is pithed and the heart exposed by removing a circular piece of the carapace. The two tracheae are exposed and a branched cannula introduced. The cannula is connected to a pressure bottle or respiratory apparatus in order to maintain a constant pressure within the carapace and thus to promote a steady return of the venous blood to the heart. This ensures a

complete filling of the ventricle and maintains a satisfactory flow through the coronary arteries. The pericardium being opened, the vessels are observed through a microscope, provided with a No. 1 eyepiece and a 2 inch objective. This combination gives a magnification of seventeen times, is sufficient to clearly display the blood flow in the larger arteries and veins, and is just sufficient to enable the individual corpuscles to be seen passing through the capillaries.

The heart of the tortoise is provided with a single coronary artery, which, springing from the aorta high up and passing directly downwards along its right surface, quickly divides into two main branches. These two main branches, one going to the left and the other to the right, encircle the base of the ventricle, and divide into one or more larger branches and several smaller ones which extend down on the dorsal and ventral surface of the ventricle. The arteries on the surface of the ventricle divide or send off a few branches, and these, while still of good size, dip and penetrate into the musculature. Very small arteries are rarely to be seen on the surface of the ventricle. Two small arteries course towards the head from the main ventral circular vessel at the base of the ventricle and supply the beginning of the pulmonary artery and aorta. In the exposed tortoise heart the pulmonary artery lies to the left and slightly ventral to the aorta as in higher animals. One of the arteries (about 0.06-0.1 mm. in diameter) runs on the left lateral aspect of the pulmonary artery, while the other and slightly larger one passes up the vessels in the sulcus between the aorta and the pulmonary artery; these two arteries give off lateral branches which divide and sub-divide into smaller arterioles. The arterioles which passed across the ventral surface of the pulmonary artery have been selected for study, as this artery is easily pulled forward and made relatively stationary by means of a small stitch in its pericardial attachment. A very satisfactory microscopic field is thus obtained since the wall of the pulmonary artery, when well illuminated, forms a brilliant background against which arteries, capillaries and venules stand out; in this field the circulation of the blood can easily be studied in detail. The arteries supplying the ventricle can also be well studied by this method, although the movements of systole cannot be so fully eliminated; the size of, and the blood flow in, the superficial vessels can be determined easily.

The blood is collected into veins which usually accompany the arteries. It may be added that the veins are less sinuous than the arteries and are redder in colour, the latter having a bluish tinge. When a vein crosses an artery it usually passes deep to the latter. The veins empty into vessels which encircle the base of the ventricle and flow into the coronary vein.

The influence of the heart beat on the blood flow in the coronary arteries and veins which, so far as is known, has not hitherto been studied under the microscope, is well seen in this tortoise preparation. The flow in the arteries, arterioles and venules lying on the pulmonary artery and aorta is greatest during systole, and gradually decreases throughout diastole, but

the flow is continuous throughout the whole cardiac cycle. In the superficial arteries supplying the ventricle, if these dip into the musculature, the rate of flow decreases with the onset of systole, and as the muscle hardens is often brought to a standstill: not infrequently, the arterial blood flow may actually be reversed towards the end of systole. In early diastole, the flow is very rapid, and subsequently decreases up to the onset of the next systole. On occasions, however, a superficial artery is seen which communicates directly with a superficial vein. Under these circumstances the flow is similar to that seen in the vessels lying on the pulmonary artery and aorta.

In the veins which emerge from the ventricular muscle and pass directly to the circular vein at the base, the blood flows in very rapidly at the beginning of systole, stops momentarily at the end of systole, and flows again, though slowly, during diastole. If superficial venous anastomoses are very free, the flow changes are often more complex and difficult to unravel.

The action of adrenalin. The action of Park Davies and Company's adrenalin chloride placed directly on the coronary arteries has been studied on thirteen tortoises. The usual dilution employed has been 1 in 10,000, which was obtained by diluting the B.P. 1 in 1,000 solution ten times with alkaline Ringer's solution.* In a few instances a 1 in 1,000 or 1 in 100,000 concentration has been employed. The solution is applied to the artery under observation by picking up a minute drop on the end of a fine glass rod and lowering it until the drop just touches the tissue and detaches itself. If, however, a single drop is found to spread, a small piece of filter paper or cotton wool soaked in the solution is gently placed on the desired spot and maintained upon it for a minute or two. Care is taken that little pressure or friction† is exerted on the tissues; usually the glass rod does not touch the tissues. Observations have, for the most part, been made on the action of adrenalin on the vessels of the pulmonary artery. These vessels belong to the coronary system but, lying as they do on the pulmonary artery, are, strictly speaking, vaso-vasora. They are, however, in all probability provided with the same nerve supply as the coronary vessels supplying the ventricle, and similar reactions should be obtained from both sets of vessels. In another series of observations the vessels of the ventricle itself have been similarly investigated.

A typical reaction of the arteries lying on the pulmonary artery to a drop of adrenalin solution has been obtained in eleven out of thirteen tortoises. Within two minutes of applying the drop, the artery becomes definitely constricted and the blood flow in it ceases: often large portions of the artery disappear and its course is indicated in those parts only where

* The *Ph.* of this solution was under 8.0.

† Deliberate mechanical stimulation of the artery with the glass rod often gives rise to definite local constriction, which passes off within a few minutes. It is easily differentiated from the long lasting and more diffuse constriction produced by adrenalin.

corpuseles are trapped. Frequently within one minute the vessel is thought to be constricted, but a slight degree of constriction is difficult to estimate, and it is only when the constriction becomes well advanced that a confident judgment on the reaction can be formed. A similar reaction is often seen in neighbouring arteries, but it is delayed and is ascribed to surface spread of the adrenalin solution. The constriction so produced persists ordinarily for from 45 to 90 minutes. In occasional instances the action is seen to be more fleeting, the blood flow being again observed after three to five minutes and the artery soon returning to its normal dimensions. Whether the constriction is fleeting or, as is more usual, prolonged, the vessel always regains its original calibre and can then be constricted again by a further application of the drug. The diameter of the arteries studied in these observations has varied from 0.01-0.1 mm.. The adrenalin reaction on the main branch, which runs on to the pulmonary artery from the coronary vessel, and the diameter of which is about 0.1 mm., is not as striking or as constant as on the smaller end branches particularly studied. In most instances a definite constriction has been observed, and in four animals this main artery has been seen at some time during the experiment to be entirely closed as far back as its point of origin. In two tortoises, however, no apparent change in the size of the vessel could be detected, possibly because the solution failed to reach it—it is more deeply covered than its end branches—or possibly because its susceptibility to adrenalin has the same local variation as has been described by Krogh in the arteries of the frog's tongue.

The arteries on the ventricles have been studied in five tortoises, the diameters of these vessels varying from 0.04-0.14 mm.. A number of vessels has been tested on each ventricle and in most of the animals good constriction in response to adrenalin, in 1 to 10,000 solution, has been observed. Within a minute of the application of the adrenalin, a white line develops on each side of the artery under observation, extending into and indenting the artery here and there. As the constriction progresses the white line on each side becomes more definite, the lumen narrower; in some instances the blood disappears from the lumen and the original course of the vessel is marked by a ribbon like white line. The reaction is completed in three to ten minutes, and persists as long as $1\frac{1}{2}$ hours. The neighbouring vessels are sometimes similarly affected, but in them the reaction is delayed. The degree of constriction, however, ordinarily to be observed is rarely as great as in the small vessels of the pulmonary artery. In this connection it may be recalled that the main arteries on the pulmonary artery do not seem to respond so well as the smaller branches.

Effect of vagal stimulation. The action of vagal stimulation upon the coronary vessels of the pulmonary artery and of the ventricle itself has been studied. Both vagi were exposed and kept moist. They were stimulated by a faradising current of sufficient strength either to slow or to completely arrest the naturally beating heart. The ventricle was driven rhythmically

throughout the observation at a rate slightly above the natural heart rate, so that as far as possible the supply of blood to the coronaries might be maintained. We have been unable to observe any change in size in the normal vessel when the vagi were stimulated, but, as has been pointed out, slight changes in the calibre cannot be detected with any certainty. If, however, the artery has previously been constricted by adrenalin, vagal stimulation invariably dilates the vessel. An arteriole on the pulmonary artery is completely constricted by adrenalin so that it practically disappears and is closely observed for a period of 5 to 10 minutes to detect any possible change; if, at the end of this period, the condition of the artery appears constant, either the right or left vagus is stimulated. The duration of vagal stimulation varies from 2 to 4 minutes. Usually within 2 minutes after the onset of vagal stimulation the artery again becomes apparent, the blood begins to flow in it and in many instances the vessel opens quickly to its original size. After the withdrawal of the stimulation the artery constricts again and becomes invisible, though this by no means invariably happens. When it does happen dilatation can repeatedly be induced in the same vessel. On the occasions when reclosure does not occur the vessel can be constricted again with adrenalin; to be opened once more by vagal stimulation. In no instances have we failed to open a constricted vessel by one or more vagal stimulations, though on occasion a first and more rarely a second stimulation has been unsuccessful; initial failure is commonest when stimulation follows soon after the vessel has been closed by adrenalin.

The vessels of the ventricle have been similarly investigated and with similar results.

In two of our tortoises a cannula has been introduced into the carotid artery and the blood pressure observed by means of a mercurial manometer. The initial blood pressures averaged 50 mm. Hg.. During vagal stimulation the pressure fell about 2 mm. Hg., gradually returning to its former level after the withdrawal of vagal stimulation. These observations have been undertaken under the usual conditions of our experiments, namely, with a ventricle responding throughout to regular induction shocks, with a view to excluding change in the general blood pressure as a cause of the coronary reaction.

Effects of vagal stimulation after atropine. In two tortoises 0.1 cc. of a 0.1 per cent. solution of atropine has been injected intravenously, a dose found to be sufficient to prevent vagal inhibition. An arteriole on the pulmonary vessel has then been constricted in the usual way by adrenalin and repeated vagal stimulation has failed to induce dilatation, although the current strength used has been greater than that required to produce complete cardiac standstill in the animal before atropinisation. In both these tortoises, either before atropinisation or after the atropine reaction had passed off, the arteries constricted to adrenalin and opened up on subsequent vagal stimulation.

In two other tortoises 0.1 per cent. atropine was applied locally to arteries already constricted by adrenalin. Under these circumstances vagal stimulation occasionally opened the vessel. If, however, 1 in 1,000 adrenalin solution was diluted to 1 in 10,000 by adding 0.1 per cent. atropine Ringer and then applied to the vessel, the constriction which followed could not be influenced by vagal stimulation. These statements apply both to the vessels supplying the pulmonary artery and to those coursing on the ventricle.

SUMMARY.

In the tortoise heart beating *in situ*, adrenalin in a dilution of 1 to 10,000, or even to 1 to 100,000 applied directly to branches of the coronary arteries unmistakably constricts these vessels. The finer arterial branches appear to be more susceptible than the larger ones, giving more constant effects and constriction of a more uniform degree along the course of the vessel. The constriction is long lasting, but, gradually passing off, may be repeated when the drug is reapplied. Arteries so constricted can usually be opened up to their full extent by stimulation of the right or left vagus nerve. Constriction returns, often though not invariably, when the effect of vagal stimulation subsides: in such instances dilatation can be induced again by restimulation of the vagus. These effects do not result from change in blood pressure or from altered heart rate. General or local atropinisation of the animal abolishes the vagal reaction. The observations here recorded have been repeatedly and successfully demonstrated to other workers in the laboratory.

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SINO-AURICULAR HEART BLOCK IN A DOG SUFFERING FROM EXPERIMENTAL STREPTOCOCCUS ENDOCARDITIS.

PAUL S. BARKER and RALPH A. KINSELLA.

(*From the Department of Internal Medicine, Washington University School of
Medicine, St. Louis.*)

SINO-AURICULAR heart block in its simplest recognisable form consists of occasional dropped beats of the whole heart, auricles and ventricles, thus producing pauses approximately equalling two complete cardiac cycles. It was first graphically recorded by Mackenzie⁸ in 1902. Wenckebach¹¹ in 1906 attributed this disturbance to the blocking of the normal rhythmic impulse in passing between sinus and auricle. His explanation, in so far as it is here stated, is now generally accepted, but, as Lewis⁶ has pointed out, this acceptance can at present be only provisional, chiefly because of "our inability to recognise an anatomical or physiological basis for a block in this region of the mammalian heart."

The anatomical connection of the sino-auricular node with the auricle is diffuse. Lewis⁶ has shown that the impulse arising in the node spreads in all directions. Experimental work^{1, 3, 4} on mammals demonstrates that blocks between sino-auricular node and auricle are not produced until the node is surrounded on all sides by injured tissue. Such experiments, however, will scarcely explain the usual clinical condition, which is most common after digitalis administration^{2, 7} and in healthy young people^{6, 12}. It is frequently associated with impaired auriculo-ventricular condition and is probably often due to increased vagal tone^{6, 9}. While it occasionally occurs in the subjects of heart disease, sino-auricular block in itself is not usually regarded as a sign of disease^{2, 10}.

Sino-auricular block due to demonstrable disease of the tissues about the sino-auricular node has not been reported; presumably lesions extensive enough to surround the node are rarely the cause. Such lesions have recently been found by us in a dog which had sino-auricular block; while an anatomical basis for the block is apparent in this instance, it is distinctly not implied that sino-auricular block as commonly observed in man is

produced in this way. The dog was the subject of an experimental streptococcus endocarditis⁵. After injuring the mitral valve by means of a valvulotome passed into the heart through the left common carotid artery, the animal was infected intravenously with streptococcus viridans. There was a loud systolic murmur over the entire precordium, and abundant evidence of streptococcus viridans endocarditis, including positive blood cultures. The electrocardiograms taken on the 19th, 20th and 21st days after infection show sino-auricular block. Death occurred on the 25th day.

Excepting a slight respiratory arrhythmia, the most common irregularity is a simple intermission of the whole heart, giving a long pause equalling approximately two normal cardiac cycles. Occasionally this pause is longer, being about two and one-half times the normal cycle, and it is then sometimes followed by a cycle which is one and one-half times the normal. At other times, during the long pause, a single escape of the ventricles occurs. Occasionally two successive ventricular escapes are seen. In these escaped beats no auricular waves are distinguishable, and their time relations do not suggest that they are ventricular responses to impulses arising in the sino-auricular node and failing to reach the auricles. They are unlike the normal ventricular complexes, and appear to arise in the left ventricle. They are not premature. Curves of these irregularities are shown in Fig. 1 in the order described. The *P-R* interval is normal.

At autopsy there were numerous petechial spots over the skin of the abdomen, in the muscles everywhere, and in the pleuræ, pericardium, and peritoneum. The lungs showed recent multiple small infarctions. Vegetations were present on the mitral valve. The other valves were normal. The wall of the right atrium showed conspicuous oedema, especially in the region of the sulcus terminalis. Mural endocarditis was beginning in the right atrium. Evidence that the right side of the heart had been injured at the operation did not exist.

Microscopic sections reveal a considerable and rather diffuse infiltration of the wall of the right atrium by lymphocytes and large mononuclear cells, and separation of the muscle cells by oedema. The infiltration is not limited to the interstitial tissue, but also involves the muscle cells in many places. Occasional polymorphonuclear leucocytes are seen. The intensity of the reaction varies from place to place. Where the reaction is more intense the muscle cells are widely separated and some destroyed; in many there is moderate granular degeneration, and in most places the transverse striation is lost; in some places the nuclei are pyknotic. There is no increase in connective tissue, excepting about some of the smaller arteries, where the increase is slight. This lesion (Fig. 2) is present in varying degree on all sides of the sino-auricular node, which is thus completely surrounded by diseased tissue. The node itself appears almost normal (Fig. 3). The ventricular muscle shows slight granular degeneration and a few small foci of lymphocytic infiltration.

SUMMARY.

A dog suffering from experimental streptococcus endocarditis developed sino-auricular block shortly before death.

Post-mortem an inflammatory process was seen to involve the wall of the right atrium on all sides of the sino-auricular node. The node itself appeared normal.

Although an anatomical basis for sino-auricular block is evident in this isolated case, it is not implied that sino-auricular block as commonly observed in man arises in this fashion.

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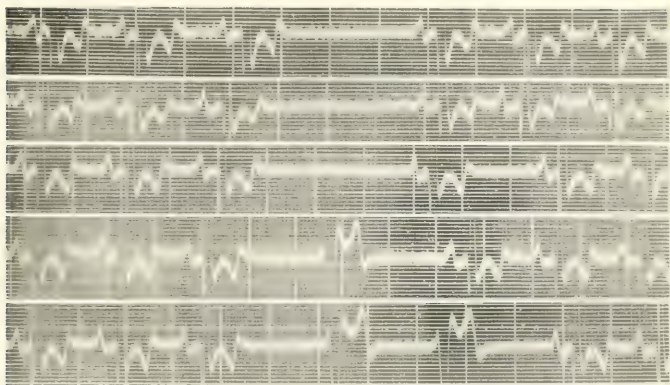


Fig. 1. Sinoparasympathetic block with variations and ventricular escapes as described in the text. Lead *II*. Time, 0.2 sec.

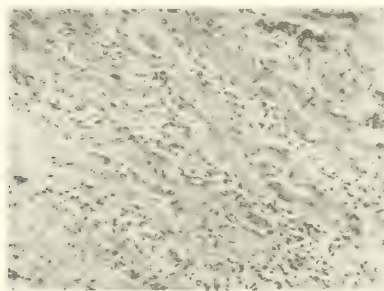


Fig. 2. Wall of right atrium near sinoauricular node. $\times 150$.

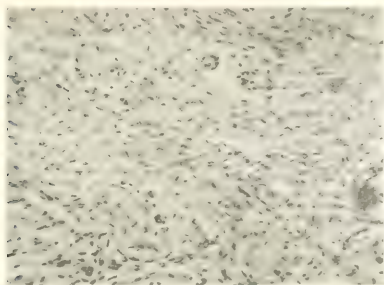


Fig. 3. Sinoauricular node. $\times 150$.

NOTES ON THE ACTION OF CERTAIN DRUGS IN CLINICAL FLUTTER.

By A. M. WEDD.

(From the Mercy Hospital, Pittsburgh.)

THESE observations are taken from a study of twelve cases of pure flutter and are of interest in their relation to a simple circus movement as the basis of this disorder. Almost with its recognition as a separate mechanism two important therapeutic facts were ascertained, namely, that experimental flutter could be converted to fibrillation by vagal stimulation and that by the administration of digitalis clinical flutter was usually converted into fibrillation, following which the normal rhythm frequently reasserted itself.

Digitalis.—The changes produced by digitalis in this series are given in Table I. The change of auricular movement is seen to be small as a rule and to occur in either direction, although the general tendency seems to be toward an increase of rate. The final effect on the flutter cannot be predicted from the initial change in auricular rate, but no definite conclusion should be drawn, since changes often occur suddenly and the interval between records in these cases was usually 15 to 24 hours. In *Case 1*, on two occasions, an increase in rate occurred before the auricle fibrillated: observation *c* was made two years later and a different digitalis preparation was used; no change in auricular rate was recorded before the onset of fibrillation in this instance. In *Cases 3* and *13 (b)* an initial rise was followed by a subsequent fall of rate before the onset of fibrillation. No records were taken in *Case 2* before digitalis was given, but as 242 beats per minute is an unusually low rate for flutter it seems probable that the action throughout was to lower the rate. In this case several courses of digitalis failed to produce fibrillation: only high-grade A-V block resulted. Likewise in *Case 5* there was a fall in auricular rate and normal rhythm appeared, but a period of fibrillation during the 15 hours between examinations cannot be excluded. This case is especially interesting, for the digitalis-atropine reactions (Table II) after the onset of the normal rhythm show the usual dual action of digitalis on the A-V node. In a recent study of the action of digitalis on the fibrillating auricle³ it was found that with full therapeutic doses an increase in auricular

TABLE I.
Action of digitalis on flutter.

Case.	Rate before digitalis.		Digitalis administered.		Rate after digitalis.	
	auricle	ventricle	cc.	time	auricle	ventricle
1 <i>a</i>	296	116	24	2 days	303	122
			48	4 days	fibrillation	86
<i>b</i>	292	81	88	10 days	306	65
			96	11 days	fibrillation	71
<i>c</i>	282	83	86	6 days	282	70
			104	7 days	fibrillation	61
2	Not recorded		29	10/28/17	242	84
			36	11/3/17	226	56
			52	11/9/17	228	57
			0	12/7/17	230	115
3	286	143	57	5 days	294	98
			69	6 days	288	72
			81	7 days	fibrillation	66
4	Normal rhythm	80	25*	4 days	206	68
5	275	83	21.5	2 days	264	66
			29	3 days	Normal	81
10	260	130	30 cc.	3 days	286	105
11	316	79	8 cc.	2 hrs.	300	70
			24 cc.	3 days	308	74
13 <i>a</i>	308	154	24 cc.	3 days	300	118
			24 cc.	3 days	329	84
			34 cc.	4 days	320	80
			40 cc.	5 days	fibrillation	76

* 1 mg. strophanthin plus 25 cc. tincture.

† Reading 4 days after end of 1st course of digitalis.

TABLE II.
Reactions to digitalis and atropine in Case 5

Date.	Aur. rate.	Vent. rate.	Drug.	Block.
May 5	Norm. mech.	75		<i>P. R.</i> - 0-20
June 7	275	83		3 : 1—6 : 1
June 7	264	132	Atropine 2 mg.	2 : 1
June 9	264	80	Tr. dig. 11.5 cc.	3 : 1—5 : 1
June 10	264	66	Tr. dig. 21.5 cc.	4 : 1
June 11	Norm. mech.	81	Tr. dig. 29 cc.	<i>P. R.</i> —0-24
June 11	99	Atropine 2 mg.	<i>P. R.</i> —0-18
June 12	89	Tr. dig. 39 cc.	<i>P. R.</i> 0-40
June 12	104	Atropine 2 mg.	<i>P. R.</i> —0-24

rate usually occurs, and the possibility of a dual action of that drug on the auricle was considered, namely, that it has a direct action on the muscle which by lengthening the transmission intervals and the refractory period slows the oscillation rate, and an indirect action which by stimulating the vagal system and shortening the refractory period increases the rate of oscillations. Thus, any change in auricular rate occurring under digitalis expresses the resultant of these antagonistic influences. The failure of digitalis to alter the auricular rate may be readily explained on the basis of a circus movement, the antagonistic reactions being so balanced as to affect equally the conduction rate and the refractory period so that the gap remains unchanged, and, until some sudden change occurs to produce block on the central path, the circulating wave continues.

Atropine. Reactions to atropine are given in Table III. Records were taken at intervals of 10 or 15 minutes for one to one and a-half hours after the injection of atropine: the rates given for the period of atropinisation are those presenting the maximum change. It is recognized that the dose given (2 mg subcutaneously) is insufficient to ensure complete paralysis of the vagus, and although with such doses in cases of fibrillation the maximum ventricular rate is often obtained³ the fall in auricular rate is less than with larger doses. The results given are therefore of qualitative value and indicate the directions of the reaction rather than a complete atropine effect. The first four cases show the expected result, a slight fall in auricular rate, dependent on increased refractory period resulting from decreased vagal tone, and a rise in ventricular rate, consequent on the establishment of a 2:1 rhythm. In *Case 10* only of the series did the ventricle become responsive to more than every second auricular beat, and it so happened that this was the only case in which pure 2:1 response was present at the time when atropine was given. This passage into 1:1 response is probably not significant, for earlier when there was an irregular ventricular response pressure on the neck over the right vagus was followed by an increase in ventricular rate to 194 (the auricular rate could not be counted), which can be attributed only to emotional disturbances. In this case and in one other (*Case 12*) there was a definite increase in auricular rate. Rothberger and Winterberg⁴ have shown that in experimental flutter stimulation of the sympathetic nerves accelerates the rate and increases the force of both auricle and ventricle and, in one example given, the auricular rate increased from 556 to 569 while the ventricular rhythm increased from 3:1 to 3:2, the latter being the rhythm obtained in *Case 10* under atropine. In *Case 10*, beside the usual phenomena produced by atropine, there was mild cerebral delirium. Nothing was noticed in *Case 12* that suggested unusual sympathetic activity: exercise, walking up a flight of stairs, which was done with difficulty, caused no change in rate of either auricle or ventricle: following atropine the patient spoke without prompting of blurred vision and extreme dryness of mouth, but there were no nervous or mental changes. In *Case 11* neither

TABLE III.

*Reaction to atropine.**

Case.	Digitalis, cc.,	Rates before atropine.		Block.	Rates after atropine.		Block.
		auricle	ventricle		auricle	ventricle	
1	0	296	116	2:1—3:1	288	144	2:1
2	36	226	56	3:1—6:1	224	112	2:1
4	25	206	68	2:1—3:1	194	97	2:1
5	0	275	83	3:1—6:1	264	132	2:1
10	0	261	130	2:1	268	180	2:1, 1:1
12	?	260	52	3:1—7:1	273	68	4:1
					273	88	2:1, 3:1
11	0	324	81	4:1	324	81	4:1

* The dose being 2 mg. subcutaneously.

† Alternating phases, a half to one hour after atropine.

TABLE IV.

Summary of reactions to quinidine (maximal changes).

Case.	Digitalis, cc.,	Rates before quinidine.		Total quinidine in grammes.	Under quinidine.	
		auricle	ventricle		auricle	ventricle
9	0	268	107	1.2	228	92
11	0	309	76	0.8*	264	132
	24	308	74	1.2	234	99
				1.6	220	110
				2.2	Normal	77
12	0	250	60	0.8*	208	104
				3.2	181	91
13	0	304†	152	0.8*	256	128
				4.0	254	127
	24	300	118	0.8*	254	127
				5.6	230	115

* Single dose.

† Rates on the 17th August. The reaction to a first dose of 0.8 of a gramme and corresponding to the broken line in Fig. 1.

auricular nor the ventricular rates changed, although dryness of mouth, dilatation of pupils and blurring of vision were produced. In *Case 2* the auricular rate fell only two beats but the ventricular rate doubled. The auricular rate in *Case 11* was the highest of the series; it may be that this high rate of auricular beating prevented the usual increase in ventricular rate. The reaction in *Case 4* is of especial interest, for the auricular rate was originally low; a fall in auricular rate under atropine is valuable in differentiating a circus rhythm from a simple tachycardia.

Quinidine.—The action of quinidine sulphate was studied in four cases (Table IV). In this table the lowest rates obtained during the administration of quinidine are given: they did not always coincide with the total dose. A patient (*Case 9*), who is a druggist, would not come into the hospital; three doses each of 0.4 of a gramme of quinidine were taken at four hourly intervals; about one hour after the last dose he experienced sudden weakness, profuse perspiration, blurring of vision, ringing in the head and a sense of mental exaltation which he said was similar to that once felt after a large dose of cocaine; he became very cyanotic, the heart beat rapidly and finally diarrhoea supervened. After two hours the symptoms began to abate and the next morning the patient felt as well as usual. An electrocardiogram was taken 15 hours after the last dose of quinidine. Judging from the usual speed at which the auricular rate recovers after quinidine, the fall of auricular rate produced must have been exceptional, and very probably led at the time of his attack to 1:1 response of the ventricle. In *Case 12*, a single dose of 0.8 of a gramme of quinidine was first given and then the drug was administered irregularly so as to produce the greatest lowering of auricular rate. The principal reactions are shown in Table V. The patient received in all 3.2 grammes and became toxic six hours after the last dose had been given: the symptoms were restlessness, profuse perspiration, exhaustion and a feeling that the heart would stop beating. The flutter continued and on the following day the patient left hospital. In *Case 11*, a single dose of 0.8 of a gramme was given and at the end of two hours the auricular rate had fallen from 309 to 264 and the ventricular rate had increased from 76 to 132. Because of palpitation during the period of rapid ventricular beating it was decided to give digitalis before proceeding with quinidine, and 24 cc. of tincture were administered in three days: this produced nausea. Three doses of 0.4 of a gramme of quinidine were then given during the night and a fourth dose at noon on the next day. One and one-half hours later the auricular rate was 220 and the ventricular 110. During the night three doses of 0.2 of a gramme were given and on the following morning the mechanism was normal (see Table IV). In *Case 13*, quinidine was given according to the plan indicated in *Case 12* and the principal results in this case are given in Table VI. The reactions to a single dose of 0.8 of a gramme are shown in Fig. 1 (broken curve). On August 20th and 21st 2 grammes were given in 18 hours, and the auricular rate fell from 308 to

TABLE V.
Quinidine reactions in Case 12.

Day.	Hour.	Doses of quinidine.	Auricular rate.	Ventricular rate.
June 24	9:45	Quinidine sulphate 0.8 gm.	250	60
	9:50			
	11:50		229	68
June 25	12:50		208	104
	11:00		234	61
June 26	4:00 and 10:00 p.m.	Quinidine 0.4 gm.		
	6:00	Quinidine 0.4 gm.		
	11:00		196	65
	11:30	Quinidine 0.4 gm.		
	12:00		190	70
	12:30		181	91
	2:15		193	96
	3:45	Quinidine 0.4 gm.		
	5:20		188	83
	11:00	Quinidine 0.2 gm.		
June 27	6:00	Quinidine 0.2 gm.		
	11:40		192	90
	1:30		212	98

TABLE VI.
Quinidine reactions, Case 13.

Day.	Hour.	Doses of quinidine.	Auricular rate.	Ventricular rate.
<i>Before digitalis.</i>				
Aug. 20	10:00		308	154
	6:00 and 12:00 p.m.	Quinidine sulphate 0.4 gm.		
Aug. 21	6:00	Quinidine 0.4 gm.		
	9:30		282	141
	9:35	Quinidine 0.4 gm.		
	11:30		266	133
	12:00	Quinidine 0.4 gm.		
	3:00		254	127
<i>After digitalis.</i> Aug. 28	4:00		260	130
	10:00		300	118
		Quinidine 2.2 gm.*		
Aug. 29	3:50	Quinidine 2.0 gm.*	248	124
Aug. 31	9:30		272	136
	10:35	Quinidine 0.6 gm.		
	12:00		248	124
	1:00	Quinidine 0.4 gm.		
	2:00		240	120
	2:30		236	118
	3:00		234	117
	3:45	Quinidine 0.4 gm.		
	4:45		230	115
	5:15		244	122

*Total quantity given between the stated time intervals.

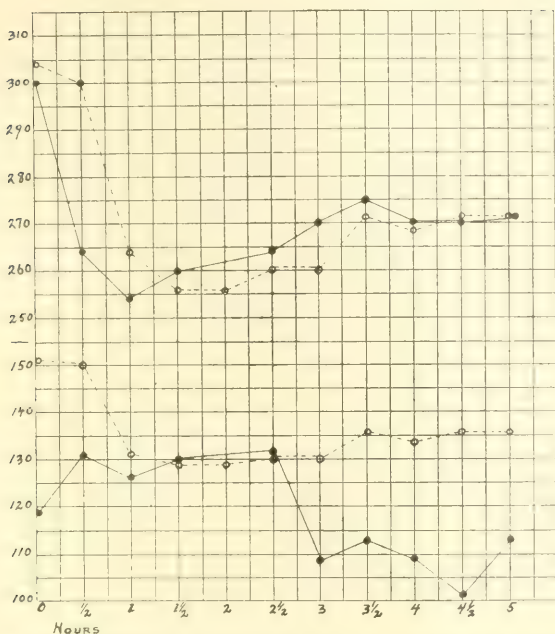


Fig. 1. Case XIII. Reactions to a single dose of 0.8 of a gramme of quinidine sulphate. Solid line, post digitalis curves.

254, a 2:1 block being maintained, and the blood pressure having fallen from 130-90 to 100-60, the height of the *R* waves in lead *II* varied phasically and inequality in the strength of the radial beats appeared. Further quinidine was given on two succeeding days, but the lowest auricular rate attained was 258. Tincture of digitalis, 24 cc. in three days, was then given and quinidine repeated. The lowest auricular rate that could be obtained was 230. The patient wished to leave the hospital as soon as possible, and so, after an interval of eight days during which a total of 5.6 grammes of quinidine had been given without affecting the flutter, digitalis was resumed; 40 cc. were taken in 5 days before fibrillation supervened. Two days later the rhythm was normal.

The combined action of quinidine and digitalis studied in *Case 13* is of special interest. In Fig. 1 are shown the reactions to two single doses of 0.8 of a gramme of quinidine, the one given before and the other after 24 cc. of tincture of digitalis. Following digitalis, the total fall in auricular rate

under quinidine was the same as in the control observation; in fact the two auricular curves are almost identical: the chief evidence is found in the ventricular curves: the ventricle responded irregularly 3 hours after quinidine had been given and not at half the auricular rate, and thus the ventricular rate was controlled by the digitalis. The other quinidine observations, before and after digitalis, are not strictly comparable in time or total quantity of the drug, but before digitalis the lowest auricular rate reached under quinidine was 254, 1·2 grammes having been given in six hours: because of fall in blood pressure, change in the form of ventricular complexes and irregularity of the volume of the pulse, it was felt unwise to give further quinidine when that rate-level had been reached. After digitalis a fall in auricular rate to 230 was produced by quinidine. In *Case 11*, before digitalis, a single dose of 0·8 of a gramme of quinidine was given and, after digitalis, three doses of 0·4 of a gramme were given during the night; these proceedings are not, of course, comparable, but the greater slowing after digitalis (30 beats) is striking.* The foregoing observations suggest that a greater lowering of auricular rate can be obtained by quinidine if the heart is first digitalised.

It has been pointed out in *Cases 12* and *13* that, after quinidine, certain lowered auricular rates were obtained and that additional quinidine did not produce further lowering. These results agree with what is now well known, that in particular cases minimal levels are reached in flutter, which cannot be passed. In a case reported by Levy² in which the transition from flutter to normal rhythm was recorded, slight lengthening of the cycles just preceding the break occurred, but as Levy expressed it, the abruptness of change was remarkable.

Until the recent introduction of quinidine into therapeutics the accepted treatment of flutter was the administration of digitalis until fibrillation supervened: the drug was then stopped and in many cases, after varying periods of time, normal rhythm was again established. In three out of four cases of this series fibrillation so produced was persistent. It is now clear that a transitional stage of fibrillation is not essential to the restoration of normal rhythm and, in the treatment of flutter, it should be avoided if possible. From the foregoing observations it would seem that the use of quinidine, or a combination of digitalis and quinidine, using the former in a quantity short of that which will produce fibrillation, may give the desired result. There seems to be confusion regarding the action of these two drugs and their possible antagonistic properties: thus in a recent paper, Hart¹ appears to base his conception of antagonism on the rise of ventricular rate following quinidine without taking into account the lowered auricular rate. Each drug has a dual action on ventricular rate, the vagal elements alone are antagonistic while the direct actions are synergistic. In two instances lower rates of auricular beating were obtained by combining the two drugs, and this

* The more so since (as in *Case 13*) a single dose of 0·8 of a gramme is usually more potent than are three separate doses of 0·4 of a gramme.

would seem to be desirable since a lengthened refractory period tends to destroy the circus movement. The value of previous digitalis medication in protecting the ventricle from an excessive increase in rate under quinidine, already pointed out for fibrillation³, is likewise seen in these cases. In *Case 12* quinidine alone failed to break the flutter and in *Case 13* the combination failed. But the very nature of a circus rhythm is such that an element of chance prevails in attempting to break it up, and this is borne out in the experiences of converting fibrillation to normal rhythm by using quinidine; failure may be followed by success on a second or third trial, even with a smaller dosage than was first used. Considering all the factors, it is believed that the combined digitalis-quinidine medication administered in *Cases 11* and *13* is rational; from the standpoint of therapeutics, *Case 11* stands out as the most satisfactory of the series.

SUMMARY.

1. The action of digitalis, atropine and quinidine in clinical auricular flutter has been studied and the results found to be consistent with the theory of a circus rhythm as the underlying cause of flutter.

2. The changes produced by digitalis are variable, the reaction being a complex one depending on the dual action of that drug.

3. After atropine, the auricular rate may fall or it may increase. The ventricle tends to respond at a half rhythm.

4. Quinidine produces a fall of auricular rate: the change in ventricular rate depends on its initial rate of beating, it may rise or fall, but tends to maintain a 2:1 rhythm. A greater lowering of auricular rate by quinidine was obtained under digitalis than without it in two cases.

5. It is suggested that in treating flutter the production of fibrillation should be avoided and, by the combined use of quinidine and digitalis or by following digitalis by quinidine, to attempt to break up the circus rhythm by raising the refractory period of the muscle.

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THE DEVELOPMENT AND PROPAGATION OF THE EXCITATORY PROCESS IN THE PERFUSED HEART.

By E. COWLES ANDRUS and EDWARD P. CARTER.

(From the Cardiographic Laboratory of the Johns Hopkins Hospital and
University.)

ANY hypothesis relating to the origin of the heart beat should explain the several properties of cardiac muscle. It should explain an inherent "automaticity" which, under normal conditions, is singularly constant yet subject to reflex acceleration or retardation. It must also interpret the process involved in the "conduction" of the rhythmic impulse to different portions of the heart.

Historical.

The conclusions of most physiologists who have investigated the origin of the cardiac rhythm have this in common, they indicate that the beat of the heart is in some way dependent upon the composition of the fluid bathing its tissues. The evidence begins with the prediction of Haller⁵, in 1757: "Whosoever considers the results of these experiments of ours cannot but agree with us that the cause which excites the heart to motion lies altogether in the venous blood."

The work of Merunowicz¹⁵ and of Ringer¹⁹ pointed to the importance of the inorganic constituents in the perfusion fluid. With this phase of the problem the studies of Locke¹³, Howell¹⁰, Mines¹⁵, and A. J. Clark⁴ were prominently concerned. Langendorff¹¹, in 1884, suggested that the stimulus for the rhythm of the heart arises in the products of its tissue metabolism, a view later adopted by Engelmann⁷. Though these authors did not attempt to isolate the particular substances involved, their idea was apparently a pregnant one. Mines, in 1912¹⁶, supposed that "some essential part of the excitatory or contractile mechanism of the heart involves certain surfaces or membranes whose differential ionic permeability must be kept at or near a certain value. Since, other things being equal, the permeability of the membrane depends upon its electric charge, the electric charge must be kept at or near a certain value." Later, Mines¹⁷ conceived that the abnormalities of contraction resulting from over-rapid stimulation were incident to the local accumulation of lactic acid.

Clark¹, working upon the heart of the frog, pointed to the necessity of maintaining the hydrogen ion concentration of the perfusate between $10^{-6.7}$ and $10^{-8.5}$. Daly and Clark⁶ reported that in the frog's heart the effect of "feebly acid" Ringer's solution is to reduce the force of the beat and greatly to impair conduction from auricle to ventricle. Mines¹⁸ recorded slowing of the frog's heart and lengthening of the A-I' interval with solutions of hydrogen ion concentration of $10^{-5.6}$, and with one of 10^{-9} a quickening of the rate and a shortening of the conduction time. Finally Dale and Thacker⁵ demonstrated that the range of hydrogen ion concentration in which automatic rhythm develops in the frog's heart shifts towards the alkaline side as one passes in testing from the venous to the arterial end of the heart.

To summarise, it may be said to have been demonstrated that the heart is possessed of an inherent rhythmicity dependent upon the composition of the fluid bathing its tissues rather than upon the action of the extrinsic nerves. Particular importance has been attached to the concentration of sodium, calcium, and potassium ions in the perfusing fluid and, more recently, to the hydrogen ion concentration. The heart is made up of a mass of irritable, conducting, contractile tissue. In the first two of these characteristics it partakes of the properties of vital tissues in general; in the third it shows the functional response of muscle tissue to excitation.

First, we may briefly consider the process of excitation in general. The irritable cell consists of an agglomeration of organic and inorganic substances, colloid and crystalloid, in aqueous solution. Surrounding the cell is a tissue fluid of similar composition though differing from the cell content in the concentration of certain ions, particularly those of the inorganic salts. At the interface between these two phases the cell membrane acts to maintain certain differences in composition. Between the cell contents on the one hand and the tissue fluid on the other there exists a state of dynamic equilibrium. The local phenomena incident to excitation represent the displacement of this equilibrium at the excited point and, dependent upon the characteristics of this local process, the equilibrium is thereby disturbed for a certain distance around. Apparently each excited area thus serves to stimulate its neighbourhood: each point in this area stimulates a point farther on; and in this manner the excitation passes over the tissue as a wave.

The excited area may be shown to be electronegative to the remainder of the cell surface. It is this phenomenon which underlies the "action current" of excited tissue. Bernstein¹ has brought evidence to show that the electrical change passes over the tissue synchronously with the wave of excitation. Hermann⁹ has suggested that the local action current may act as an electrical stimulus upon the tissue immediately adjoining. Lillie¹² has elaborated an electrochemical theory of excitation along the lines suggested by Bernstein², Brünings³ and Hermann⁹. He regards the rate of the propagation of the excitatory process as determined by the magnitude of the action current.

Such in brief is the present conception of the excitatory process in vital tissues. Apart from peculiarities of structure and arrangement the tissue of the heart is unique in this respect only in that here the excitatory process requires no obvious external stimulus to initiate it. It appears to arise of itself and normally with remarkable constancy and regularity. The fundamental processes involved in the development and propagation of the wave of excitation are conceivably not different in the heart from those in other irritable tissues.

Experimental.

The writers have been engaged for several years in studying the cardiac rhythm and more particularly its origin. They first worked with the isolated heart of the terrapin (*Chrysemys picta*) perfused with Ringer's solution. This animal was selected for two reasons: the cold-blooded heart requires no rigid regulation of temperature, and is of simpler structure than the mammalian heart. The effects of altering the ionic content of the perfusate were studied, and particular attention devoted to the results of changing the P_{H}^* of the fluid. Galvanometric records were taken and the intervals carefully measured. Variations in hydrogen ion concentration were made on either side of the normal P_H of 7.4. In no case, however, was a perfusate employed which was less alkaline than P_H 7.1 or more so than P_H 7.8.

The results of many such experiments are illustrated in the accompanying tables and figures. From these it is seen that a change from a more alkaline to a less alkaline perfusing fluid is accompanied by a definite slowing of the rate and that shifting to a perfusate of higher P_H results in a more rapid rhythm. Thus in experiment No. 22, represented in Table I, while Ringer's solution P_H 7.4 was flowing through the preparation, the *R-R* interval as measured on the electrocardiographic record, was 1.32 seconds. With a perfusate differing from this only slightly in reaction, namely, P_H 7.1, the *R-R* interval rose to 1.60, while with P_H 7.8 it fell to 1.24 seconds. In Fig. 1 are charted the *R-R* intervals measured in one experiment, and these illustrate that an increase in the rate followed as the fluid was made more alkaline and a decrease as it was made less so.

Coincident with these changes, as shown in Fig. 1 and in Table II, changes are observed in the *P-R* interval, representing the conduction time from auricle to ventricle. This interval is uniformly lengthened by a perfusate of P_H 7.1 and shortened by one of P_H 7.8. In other words, change to a less alkaline perfusate retards the rhythm of the heart as a whole and decreases the rate of conduction, while variation toward a more alkaline solution produces a more rapid rhythm and facilitates conduction.

$$* P_H = \log \frac{1}{C_{H^+}}.$$

More recently the hearts of dogs were isolated and perfused with Locke's solution of the following composition :—

NaCl	9.00 gm.
KCl	0.40 gm.
CaCl ₂	0.26 gm.
NaHCO ₃	0.20 gm.
Glucose	1.50 gm.
Water	to 1000.00 cc.

The chemicals used were Merck's blue label or Baker's analysed preparations and the water used was always freshly distilled. The composition of the

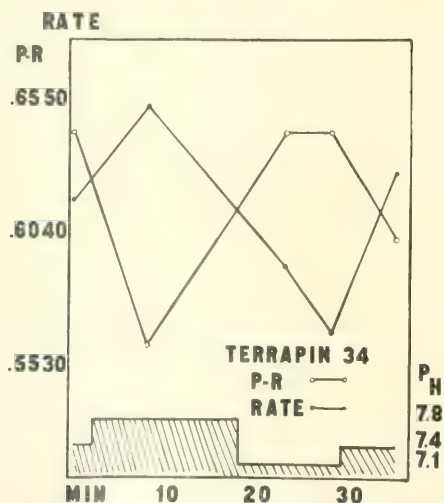


Fig. 1. Rate and *P-R* intervals showing variation with change in *P_H*.

solution was frequently checked by quantitative analysis. The reaction was adjusted by means of decinormal hydrochloric acid and sodium hydroxide, and was measured against a carefully calibrated series of indicators. The *P_H* of the solutions was rigidly controlled and was periodically checked during each experiment.

The heart was isolated by the following procedure :—The animal was fully anaesthetised with ether. The bony thorax was exposed through a midline incision and the internal mammary vessels tied through an opening in the first interspace. Artificial respiration was begun as soon as the pleura

TABLE I.

Experiment 22.—Changes in R-R interval in the terrapin heart following changes in P_H.

Time.	P _H	R-R.
3:06	7.4	1.32
3:07	7.1	
3:11		1.46
3:17		1.52
3:31		1.60
3:37	7.8	
4:05		1.24

TABLE II.

Experiment 34. Changes in rate and conduction in the cold-blooded heart following changes in P_H.

Time.	P _H	R-R.	Rate.	P-R.
3:40	7.4	1.40	43	0.64
3:42	7.8			
3:48		1.20	50	0.56
3:58	7.1			
4:08		1.80	33	0.90
4:09	7.4			
4:15		1.32	45	0.76

was opened and was maintained as long as the pulmonary circulation remained intact. The ribs were cut and the entire front of the thorax removed. Ligatures were laid around the brachio-cephalic artery and the superior and inferior venæ cavæ. The left common carotid and left sub-clavian arteries were doubly ligated and cut. Another ligature was placed at the junction of the arch and the descending aorta. A cannula was inserted in the brachio-cephalic artery and perfusion begun. Then the ligatures about the venæ cavæ and the aorta were quickly tied, the pulmonary artery was opened and the preparation removed from the thorax. In this manner perfusion was instituted through the coronary system without interruption of the major circulation.

Perfusion was carried out under a constant pressure of oxygen at 50-80 mm. of mercury. The temperature of the perfusate was regulated by means of an electrically controlled thermostatic tank with a maximum

variation of less than one degree. By means of a specially designed three-way valve it was possible to change from one perfusate to another quickly without changing pressure. Inasmuch as the mammalian heart is extremely sensitive to oxygen deficiency every precaution was observed to assure a sufficient supply of this gas during an experiment. Records taken more than an hour after the isolation of the heart were discarded and during that period from eight to fifteen litres of oxygenated Locke's solution were passed through the preparation. Electrical records were obtained by leading off from auricular base and ventricular apex with non-polarizable electrodes of kaolin paste and copper sulphate, the apical electrode being attached by a thread of worsted.

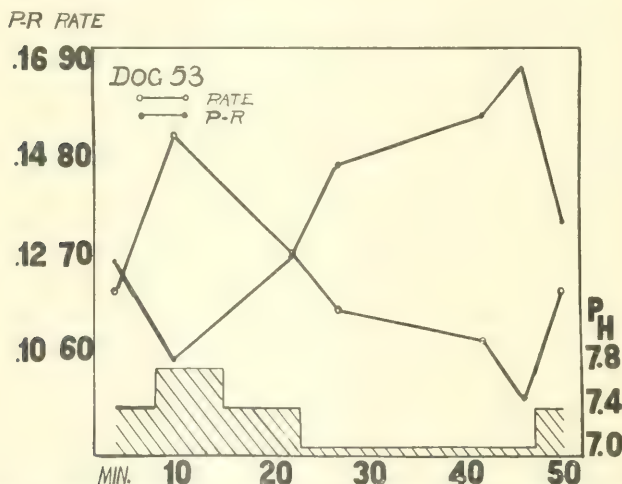


Fig. 2. Rate and P-R interval are shown to vary with P_H and in opposite directions.

In a series of over forty experiments eighteen were concerned with the effect of change in P_H of the perfusate. As with the cold-blooded heart alterations were made on either side of the normal P_H 7.4, but in no case was the heart subjected to a P_H of more than 7.8 or less than 7.0.* The resultant changes in rate, which were consistent in our experiments are illustrated by the accompanying figures and tables.

* In this connection it may be stated that when extremely alkaline perfusates containing phosphates or carbonates are used, as they have been by some previous workers, little calcium can remain in solution.

Table III summarises an experiment in which the reaction of the perfusing fluid was changed from P_H 7.2 to P_H 7.7. With such variations the rate of the sinus rhythm changes correspondingly. P_H 7.7 produces a more rapid and P_H 7.2 a less rapid rhythm than does the normal P_H 7.4. In Table IV the alterations of rate are more striking, since they correspond to greater changes in reaction, namely, P_H 7.1 to P_H 7.8. Fig. 2 illustrates the results in other experiments.

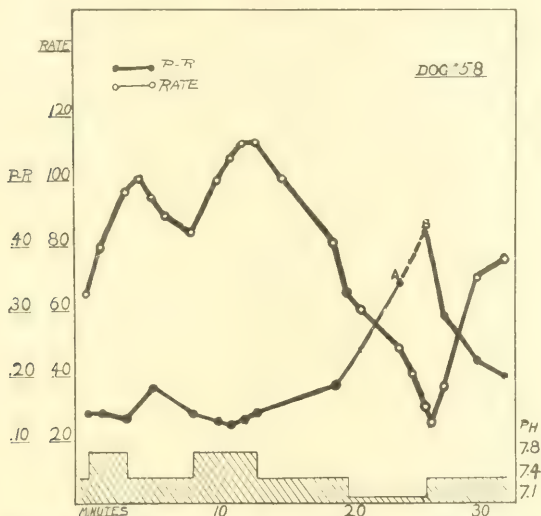


Fig. 3. Variations in rate and $P-R$ interval corresponding to changes in P_H of the perfusate. Broken line A-B represents period of complete A-V dissociation.

These effects are not confined to the sinus rhythm: they are obtainable in the presence of a nodal rhythm. For such observations the heart was isolated as described, and, after removing the pericardium, all sinus and auricular tissue was cut away. Following this operation the ventricles remained quiescent for a short interval and then began to beat with a rhythm apparently arising in the auriculo-ventricular node. It was not possible to retard this rhythm to quite the degree shown in the case of the sinus rhythm, but acceleration under a perfusion fluid with a P_H 7.8 was here more pronounced. This result corresponds to the observation of Dale and Thacker upon the frog's heart. Finally all electrical and mechanical evidence of excitation disappeared on perfusing for a protracted interval with P_H 7.0, the

TABLE III.

Changes in rate and conduction in the dog's heart following changes in P_H 7.2 to 7.7.

Time.	P_H	R. R.	Rate.	P. R.
3:20	7.4			
3:24		0.88	68	0.12
3:25	7.7			
3:26		0.80	75	0.10
3:27		0.80	75	0.10
3:30		0.72	83	0.10
3:32	7.2			
3:33		0.72	83	0.14
3:38		0.88	68	0.14
3:39	7.7			
3:41		0.76	79	0.10
3:44		0.74	81	0.11
3:45	7.2			
3:46		0.78	77	0.12
3:49		0.82	73	0.14
3:53		0.90	67	0.14
3:54	7.4			
3:59		0.84	71	0.12

rhythm being restored promptly by a normal perfusate. This effect was obtained upon both sinus and nodal rhythm.

It has been pointed out in the account of the observations upon the terrapin heart that as the P_H of the perfusate is changed, alteration in rate is accompanied by changes in conduction. Precisely the same effect was observed in the isolated, perfused mammalian heart, and this was also consistent in our experiments. In these experiments it was possible repeatedly to induce various degrees of auriculo-ventricular block, progressing in some cases to complete auriculo-ventricular dissociation, by perfusing with a solution of P_H 7.0 to 7.1, and as often to reduce such a prolonged auriculo-ventricular interval practically to normal by a change to a normal or more alkaline perfusate. An example is shown in Fig. 3 where the curve representing the P-R interval follows inversely the P_H curve below it. In the region indicated by the broken line, after the A-V interval had risen to 0.34 sec. complete dissociation developed. Following

TABLE IV.

Experiment 65. - Changes in rate and conduction in the dog's heart following changes in P_{H_2} 7.0 to 7.8.

Time.	P_{H_2}	R-R.	Rate.	P-R.
3:30	7.4			
3:48		0.80	75	0.12
3:50	7.0			
3:52		0.90	67	0.12
3:54		1.00	60	0.14
3:55		1.10	55	0.14
3:57	7.4			
3:58		0.98	62	0.12
4:02		0.88	68	0.12
4:05	7.0			
4:06		0.90	67	0.12
4:08		1.02	59	0.13
4:10		1.20	50	0.14
4:13	7.8			
4:14		1.00	60	0.10
4:16		0.94	64	0.10
4:18		0.86	70	0.11
4:20	7.4			
4:21		0.90	67	0.12
4:25		0.88	68	0.12

the return to P_{H_2} 7.4, conduction improved and the block gradually disappeared, the P-R interval falling from 0.42 to 0.18 sec.

Discussion.

The accompanying data conform to the view that the hydrogen ion concentration of the fluid bathing the cardiac tissue exercises a controlling influence upon the development and propagation of excitation therein. The more the phenomena are studied the more evident does it become that the development of the excitatory process and its propagation are inseparably linked, that no fibre can conduct the excitatory process unless it is itself excited.

The cardiac tissue represents a particular type of irritable cell, comprising an aqueous solution of colloids and crystalloids separated by the cell membrane from the tissue fluid of similar but not identical composition. The displacement of equilibrium between these two phases constitutes the excitatory process, and according to our view, in this displacement the hydrogen ion concentration of the tissue fluid is apparently an important factor. It is as though, under a normal P_H the excitability of the tissue rises to a critical level within a certain time, and, excitation taking place, the resultant disturbance is sufficiently great to set the adjacent tissue into excitation for a definite distance. With a fall in P_H two things occur:

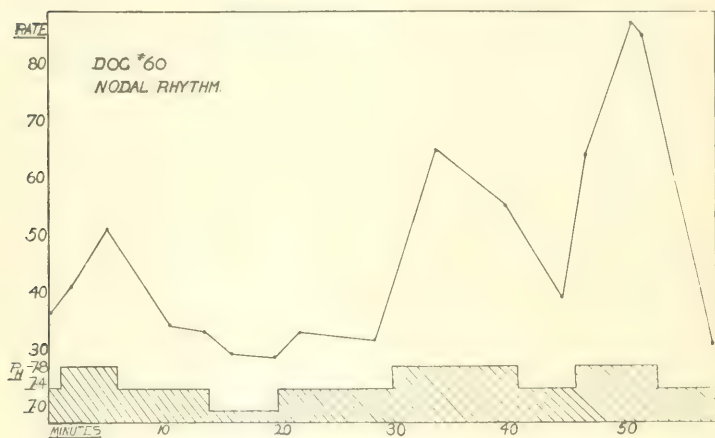


Fig. 4. Nodal rhythm showing variations in rate with alterations in reaction of the perfusing fluid.

the local excitatory process develops more slowly, and, the disturbance being less, its range as an adequate stimulus to neighbouring tissue is lessened. A slower rhythm on the one hand, and a delay in conduction on the other, result. Conversely a rise in P_H causes the excitatory process to develop more rapidly and renders it adequate to stimulate over a wider fibre. The rhythm is thus accelerated and conductivity increased. The exact mechanism whereby the P_H controls rhythm and conduction is not entirely clear, but the data herein presented are not inconsistent with the "membrane theory" elaborated by Brünings and Lillie.

CONCLUSIONS.

An account is given of a series of experiments carried out upon the perfused hearts of terrapin and dogs. It is demonstrated that in these preparations it is possible to control accurately, to accelerate and to retard, to abolish and to restore the development of the excitatory process and its propagation by changing the P_H of the perfusion fluid.

Upon the basis of these results it is suggested that the rhythm and rate of conduction in the cardiac tissue is normally determined solely, or in large part by the P_H of the surrounding fluid. It is considered that the excitatory process in the heart, as in other irritable tissues, represents a disturbance of ionic equilibrium between cell contents and tissue fluid, and that conduction is due to the direct stimulation of adjacent tissue by the disturbance so developed at the point originally excited.

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THE FORCE EXERTED BY THE MINUTE VESSELS OF THE SKIN IN CONTRACTING.

By THOMAS LEWIS.*

(*Cardiac Department, University College Hospital Medical School.*)

DURING the winter of 1915-16 and in the following spring months, with the collaboration of Drs. T. F. Cotton and J. G. Slade, I made a series of observations upon the reactions of the human skin to various stimuli². These observations led us to the very definite conclusion that the capillaries of the human skin are capable of active contraction. This conclusion was at variance with the then current views of physiologists, which were well known to us, but passive closure of the capillaries would not explain our observations, and we were able to find and quote a number of earlier observations leading to the same conclusion; observations which, though seemingly having failed to convince, appeared to us to have placed the burden of proof on those who held movements of the capillary wall to be purely passive. The publication of our paper was delayed by war conditions until January, 1917; and, on account of the same circumstances, experiments which had actually been begun on the frog's web and rabbit's ear, with a view to extending if possible our evidence of active movements of the capillary wall, had to be abandoned. They have been carried out in the interval with notable success by other workers. In October, 1917, Ebbecke⁵ published an important and independent monograph upon the same questions. This was followed by Dale and Richards' article⁴ in 1918 and in the same and following years by a series of papers by Krogh, his co-workers and others. The conclusion that capillaries are capable of active contraction† has been amply justified by this subsequent work and many new and important facts have been brought to light. These observations have lately been

* Working on behalf of the Medical Research Council.

† The conclusion as we stated it² for human skin assumed that the capillaries are responsible for skin colour. It is now recognised that the minute vessels of the skin classed by anatomists as the first plexus of *venules* are chiefly responsible for this colour; these venules have the form of giant capillaries, for like capillaries they possess no muscular coat. Strictly speaking, therefore, our evidence did not show that the actual capillaries contract actively, but that active changes in size occur in capillaries and the somewhat larger vessels into which they pour their contents, treating both types of vessels as belonging to one and the same "capillary" class. The difference may appear a small one, but it is to be mentioned in a statement which pretends to histological accuracy.

reviewed in a thorough fashion by Krogh⁷ and by Dale⁸. Recently the work of my laboratory has been directed largely towards attempts to extend that branch of our recent knowledge which concerns the activities of minute blood vessels in the human skin, and the present article and those which follow it are products of these investigations.

Force exerted in contraction.

In preliminary observations communicated to the Physiological Society⁹, it was shown that those minute vessels of the human skin which are responsible for skin colour (namely, the capillaries and especially the minute venules of the subpapillary plexus) are usually capable of resisting pressures of 50 mm. Hg. or more when they are contracted in response to the stimulus of stroking. Generally speaking, the pressures resisted cannot be displayed to surpass 50 or 60 mm. Hg.; resistance of pressure up to 90 or 100 mm. Hg. is exceptional (see Fig. 1).

The pressures which can be resisted by these small vessels is more certainly displayed, and higher readings are obtained, when adrenalin forms the stimulus to contraction. It has been shown in a previous communication that adrenalin constricts the minute vessels responsible for skin colour up to at least 1 in 30,000 dilution, and that this reaction is independent of any action on the arterioles. Carrier¹ has watched the vessels microscopically and has shown that this action is upon both the capillaries and the small venules; a conclusion which I am able to confirm. For the present observations I have employed a 1 in 1,000 solution exclusively and have obtained blanching of the skin by placing a group of small drops of the solution on the skin of the forearm, and pricking the skin through each of these with a fine needle; a circular area of blanching having a diameter of about 2-4 millimetres develops around each prick in $\frac{1}{2}$ to 1 minute and is maintained for a long while. That the vasoconstriction so produced is a more powerful one than that resulting from stroking is readily shown. If the vessels of the limb be first occluded with a Riva Rocci armlet and the skin is suitably stroked several minutes later, the white line of vascular contraction still appears; but the bright hyperæmia which follows release of the circulation invariably abolishes this white line in my experience. On the contrary, a similarly produced hyperæmia fails to wash out areas of adrenalin pallor. When the hyperæmia develops, these stand out frequently as vivid white areas on a scarlet background; in some instances, it is true, they become a little pinker in tint though remaining perfectly distinct (see footnote p. 113).

If areas of adrenalin pallor are created, and the venous pressure is then raised by placing a pneumatic pressure of 50 mm. Hg. or more on the upper arm, a fuller idea is obtained of the resisting power of the vessels concerned.

Before proceeding to describe such experiments, the accuracy of this method must be justified. If a pressure of about 60 mm. Hg. is thrown into

an armlet such as that here used and the forearm is enclosed in a plethysmograph, the curve of venous filling is usually completed in about 30 seconds or less in normal subjects. The curve rises at first relatively abruptly but rises less steeply in the later phases of filling. Does the venous pressure rise to the full height of the pressure in the armlet? To answer this question a cannula was placed in the proximal end of a vein of the forearm and connected by means of tubing, filled with 0.5 per cent. citrate of soda in normal saline, to a mercurial manometer, the zero of the mercury column being brought level with the vein. The 12 cm. pressure cuff used in the remaining observations of this paper was wrapped lightly around the upper arm, the lower edge of the cuff being brought level with the vein used. The venous pressure now registered 10 mm. Hg.; of this 8.5 mm. represented the natural venous pressure in the arm vein* and 1.5 mm. was due to the slight pressure exerted by the unexpanded armlet. The pressure in the cuff was now raised to various levels, each time from zero, and the height to which the venous pressure rose, and the time taken for each rise to complete itself, were noted and are to be seen in the accompanying table.

Cuff pressure mm. Hg.	Pressure reached in vein in mm. Hg.	Rise occurs within (in seconds).
0	10	0
22	21	15
32	32	18
40	39	30†
49	48	38
58	57	34

Thus it was demonstrated that a cuff pressure of 20 mm. of Hg., or over, quickly congests the veins below it to a corresponding point and that the cuff pressures may be used as an accurate gauge of the pressure developed in the veins. The venous pressure in the arm was raised as high as 58 mm. of Hg. within a half minute or a little longer by this method‡. Actually it was raised to a point a few millimetres short of the cuff pressure in a much shorter time period, the rise being at first rapid and the last few millimetres of rise occurring slowly, so that the very end point could not be determined accurately. These readings were taken from a patient suffering from cardiac failure with early congestion of the venous system; the inflow of blood to the arm, subsequent to a free venesection, was measured for me

* The observations were made on a patient prepared for venesection, and the arm explored lay 4 cm. below the level of the sternum, the patient lying horizontal.

† Probably a good deal over-estimated.

‡ In a second patient, suffering from auricular fibrillation and early congestion, the venous pressure was 9 mm. Hg.. When cuff pressures of 40, 54 and 72 mm. Hg. were thrown on the upper arm these pressures were all reached in a distal vein within 40 seconds. The blood pressures were 150 systolic and 95 diastolic.

by Dr. Drury (by Hewlett and Zwaluwenburg's method) at 0.71 cc. per 100 cc. of arm tissue per second. This figure represents slower filling than is usual in the normal arm.

The next table illustrates the effects of venous pressures, produced artificially by the method described upon areas previously blanched by adrenalin in a number of young normal adults. To be on the safe side the armlet pressures were maintained for periods considerably exceeding those which are actually required. Each of the numbered observations is a continuous observation upon a single subject. Thus, in the first observation

Effect of venous compression on adrenalin pallor.

Subject.	Pressure on veins		Adrenalin pallor	Brachial blood pressure.	
	in mm. Hg.,	maintained for		syst.	diast.
1	60	2 mins.	unaltered	127	88
	80	1 min. further	unaltered		
	100	2 mins. "	still distinct		
2	90	5 mins.	still present	110	75
3	80	2 mins.	unaltered	138	95
	100	2 mins. further	a little less distinct		
4	60	2 mins.	unaltered.	108	75
	80	2 mins. further	less distinct		
	98	2½ mins. "	still distinct		
5	60	2 mins.	unaltered	115	80
	80	1 min. further	unaltered		
	100	1 min. "	less distinct		
6	60	2 mins.	slightly less distinct	105	85
	80	2 mins. further	less distinct		
	90	2 mins. "	still present		

the pressure on the arm was raised to 60 mm. Hg. for 2 minutes and the areas blanched by adrenalin were seen to remain unaltered; the armlet pressure was now raised to 80 mm. for a further minute and later to 100 mm. Hg. for a further 2 minutes. At the end of the 5th minute of venous engorgement the blanched areas were still distinct, though they were less so than at lower venous pressures. Raising the venous pressure in steps is adopted to ensure full engorgement of the veins to the pressure prevailing in the armlet: it is especially necessary when armlet pressures approaching the brachial systolic blood pressure are to be used, since, when the armlet pressure is raised to a high point, the input of blood to the limb diminishes very greatly. The venous pressure can be raised much more quickly by using pressures which rise in steps, than by placing the final pressure on the armlet at once.

In the circumstances of the experiments tabulated the venous pressure is raised to 90 or 100 mm. Hg.,* the mean arterial pressure lies between these figures and the systolic pressure of the brachial artery. The minute vessels of the skin are placed between the arteries and veins. It is very probable, since adrenalin closes down the finer arterioles of the skin, that blood is by this means prevented from entering the capillaries on this the arterial side. On the venous side, owing to the extremely rich anastomoses of the subpapillary plexus, contraction of veins nearer to the heart by the adrenalin would not guard these plexus vessels from feeling the full venous pressure. Unless the venules of this plexus were actually closed, blood would enter then freely from venules of the same order, at the margins of the blanched area.† A patent subpapillary plexus, from this point of view, is to be regarded as a shallow pool of blood, the contents of which are readily displaced from side to side. That these venules are involved by the adrenalin is readily to be seen microscopically; it is also to be stated that in the forearm their contraction is undoubtedly in chief part responsible for adrenalin blanching. Thus it is clear that when contracted these minute venules are capable of resisting distending pressures of at least 90-100 mm. Hg.; they are capable of resisting pressures approaching closely to or actually reaching normal systolic pressures in the brachial artery. The important function which increased tone of the vessels in question is capable of exerting on circulatory events begins to be more apparent in the light of these figures. The function, contraction, seems to be developed to such a point that if the whole bed of minute vessels (capillaries and venules), corresponding to a large arterial territory, were to contract fully the circulation in this territory would be brought almost, if not completely, to a standstill. Having regard to the situation of the minute vessels in the cardiovascular tree, this manner of regarding them places their potential influence upon circulatory events on much the same plane as that usually ascribed to arterioles.

The minute and superficial venules have the same histological structure as have the capillaries proper: that is to say, they consist of an endothelial wall on which no muscular covering is apparent; in fact their distinction from capillaries proper is scarcely to be justified from a purely physiological standpoint. According to Spalteholz¹¹, the muscular layer is not added until the veins in the deepest layers of the skin are reached.

The only cells upon capillary walls which are known to have contractile powers are the cells originally described by Rouget¹⁰ and lately in more detail by Vimtrup¹². These are seen as isolated cells scattered on the walls of the capillaries in translucent tissues of amphibians, and each consists of a mass of nucleated protoplasm from which branched processes, encircling the

* Such venous pressures usually cause a few petechial hemorrhages in the skin of the forearm.

† When a hyperemia produced by releasing the circulation fails to flush a small area blanched by adrenalin (p. 110), this is not attributable to closed arterioles. The argument here used is valid for the first case also.

capillary, proceed. It is to be presumed that comparable cells are present upon the walls of the capillaries and venules of the human skin, though actually these have not been described. If the arrangement is similar to that on the amphibian capillary, it will be necessary to assume that most if not all of these cells are individually capable of resisting distending pressures of the order now described. That a single cell may be capable of exerting such a force is rendered more intelligible, when the minute diameter of the tubes which they encircle is borne in mind. The contractile elements will work to greater and greater advantage as the vessel is smaller.

In estimating the force which the minute vessels are capable of exerting, the circumstances in which this force is brought into play must be considered. When adrenalin is punctured into the skin, the walls of the minute vessels contract upon their contents and expel them. The pressure required to effect this expulsion is in ordinary circumstances small, since capillary pressure in vessels lying at the level of the heart is not great. *A priori*, the maximal pressure which contracted and closed vessels are able to resist is not necessarily, or even probably, a measure of the maximal pressure which the same vessels when open are capable of exerting on their contents. That this is actually so is easily shown in the case of the adrenalin reaction. If the arm is first engorged and adrenalin is subsequently pricked into the skin, blanching is rarely seen if the pressure of venous engorgement exceeds 60 mm. Hg.; usually the blanching of the skin is only just perceptible when venous pressures of 40 or 50 mm. Hg. have been previously reached. In the circumstances of the observation the vessels concerned are much dilated before they are called upon to contract: the contractile elements in their walls are thus placed at a mechanical disadvantage. Judging from the values given, it would seem evident that the minute vessels of the skin should be capable of emptying themselves in most, but not perhaps in all, physiological circumstances. The correctness of this supposition is illustrated by the following example. If in a man standing at ease adrenalin is punctured into the skin on the dorsum of the foot, blanching does not appear: if, after an interval of a few minutes, the subject lies down, the areas punctured quickly show the usual blanching. From this it is apparent that the contraction induced by adrenalin is insufficiently powerful to expel the contents of the minute vessels distended by the pressure of the column of the blood extending from heart to foot. The value of this pressure, calculated hydrostatically is about 90 mm. Hg. in a man of medium height, but Recklinghausen⁹ and Hooker⁶ have shown that the actual venous pressure in the foot does not reach the full calculated value. If, after the areas of pallor have appeared on the foot in the lying posture, the man stands up, the blanched areas remain visible, though they usually become a good deal less distinct by the time venous pressure has risen completely. If the subject now takes a few steps the venous filling of the foot decreases rapidly and the areas of blanching at once become much more vivid. It is evident therefore that the minute vessels in the skin of the foot are capable of

restraining over-distension as the upright posture is assumed, and, the body being erect, are capable of expelling their contents when they are aided by movements of the foot.

CONCLUSIONS.

The minute vessels of the human skin, which are responsible for skin colour, are capable of exerting a force when fully contracted which resists the full entry of blood into them up to pressures of at least 90 or 100 mm. Hg.. When dilated, these same vessels are able, by contracting, to expel their contents against internal pressures of at least 50 or 60 mm. Hg.. Considering their position relative to the arterial system, and the lower pressure normally developed within them, the potential power of these minute vessels to influence circulatory events by contracting, cannot be regarded as far removed from that usually ascribed to the arterioles.

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FIG. 1. Four light strokes have been made across the forearm of a young subject with the cold steel dilatometer and these have produced obliteration of the superficial and minute vessels of the skin. An armband on the upper arm has been pumped to a pressure of 70 mm. Hg., and maintained until the photograph was taken at the end of 2 minutes. Note the distension of the veins and the persistence of the areas of skin pallor.

VASCULAR REACTIONS OF THE SKIN TO INJURY.

PART I.—REACTION TO STROKING; URTICARIA FACTITIA.

By THOMAS LEWIS.*

(*Cardiac Department, University College Hospital Medical School.*)

IF the human skin is stroked firmly with a blunt point, a local reaction of the vessels follows which is visible to the naked eye. Most of the relevant and visible features of this reaction are now known. A red line appears, marking out with considerable precision the area of skin pressed upon; it begins to appear in from 3 to 18 seconds and is at its height in 30 to 50 seconds^{1, 3 & 9}. It is at first a red line, shortly acquiring a bluish tinge. The red line is due to dilatation of the capillaries and minute venules of the skin, and this dilatation is brought about by (*a*) primary dilatation of the vessels themselves, and (*b*) in part by coincident dilatation of the corresponding terminal arterioles. That both capillaries and venules are involved in the dilatation has been shown by direct microscopic examination by Carrier¹, observations readily confirmed. That it is a primary dilatation of these minute vessels is shown by the occurrence of the red line on the arm when the circulation of the limb has been brought to a complete standstill². That the arterioles are also dilated was first pointed out by Carrier, who states that the line shows red on the blue background of surrounding skin if the stroke is put down on an arm cyanosed by cold; the same holds good in an arm made blue by venous congestion, a method I have repeatedly used. In a number of subjects in whom the skin is hypersensitive, or in less sensitive skins where the stroke is very heavy, the red line is shortly followed (20-60 seconds after stimulation) by (*c*) bordering areas of erythema; this flush surrounds the red line, is of brighter red colour and has an irregular margin. It spreads for a variable distance outside the region of actual pressure. It is produced by an increased flow of blood to the skin consequent on dilatation of the skin arterioles^{7 & 9} and is reflex in origin⁹. The flush does not occur over the arm when the circulation is occluded²; it is said not to occur over anæsthetic areas in certain peripheral sensory nerve lesions³ or in certain injuries of the spinal cord⁹. Were it not doubtfully correct to regard the arteriolar dilatation (*b*) of the central red line and that of the surrounding

* Working on behalf of the Medical Research Council.

flush (c) as similar in origin, the reaction in a sensitive skin might be described by saying that a heavy stroke yields a continuous and wide reddening of the skin by reflex arteriolar dilatation, reaching often a considerable though variable distance beyond the limits of the stroke, while the capillaries and venules directly under the line of stroke also expand in more direct response to the stimulus. Even when in less sensitive skins no visible flush appears around the line of stroke, nevertheless some degree of arteriolar dilatation is usually to be displayed in the surrounding skin if the arm is first congested before it is stroked. Thus, the reactions so far described appear to be constant in quality, though variable in quantity; there are variations in the colour intensity of the central red line, there are conspicuous variations in the degree of the flush and in the area which it covers.

Finally, the region of the red line may develop swelling, in the form of a more or less pronounced urticarial wheal, a local oedema. The wheal is usually described as rare, and for this reason it has generally been regarded as pathological. It is by no means rare. As stated in a previous communication², the reactions in 84 men, mostly young and in hospital for the condition often described as "irritable" heart, were tested, and a palpable swelling of the skin as a reaction to a single firm stroke was seen in 25 per cent. of the cases; in 5 per cent. a full wheal was developed. We described the skin reaction in this type of patient as being conspicuous, though we knew that young people otherwise quite healthy not infrequently show similar reactions. Further experience tells us that the above figures may be treated as approximately true for young and normal subjects generally. A more severe injury than firm stroking, a scratch with a claw or thorn, or a blow with the lash of a whip, will raise the same type of wheal in the majority if not in all young subjects. I have found no difficulty in raising typical wheals, though a few of these have not been of full size, on the skins of 6 normal young men, repeating the simple firm stroke with a blunt point; eight or ten such strokes one over the other suffice. My colleague, Dr. Grant, has repeated this observation a larger number of times with very similar results. In this connection it is to be mentioned that a single pin prick will usually raise a small wheal in susceptible subjects, it also does so less markedly in many quite normal skins; Ebbecke³ has shown that repeated pricks over a small area calls forth a very distinct and characteristic wheal; this is easy to confirm. In the light of such evidence, it seems clear that the only abnormality displayed by the subject of so-called "factitious urticaria" is an exaggerated susceptibility of the skin to certain forms of stimulation. We have every reason for assuming that the wheal produced by stroking results from purely physiological reactions; the difference from subject to subject appears to be solely a difference of degree. These conclusions agree with those of Ebbecke. Because the wheal is a normal reaction of the skin to injury, because the changes leading up to it evidently belong to a physiological mechanism of defence, a clearer understanding of this mechanism than we now possess becomes of much importance.

The present observations have been directed particularly to determine more precisely the relation of the wheal to the associated vascular phenomena.

The wheal becomes perceptible within 1 to 3 minutes of the stroke and quickly rises to its height (usually in 3-5 minutes from the stroking): it is at first red. During the red stage the wheal itself, and the surrounding flush, present capillary pulsation. Shortly it pales, as does the surrounding flush, but still remains prominent. It lasts one or many hours. The exudate ceases to be poured out, as Ebbecke⁴ has shown, in about 5 minutes: absorption is very slow.

Relation of the wheal to arteriolar dilatation. Œdema produced by stroking the skin of the back occurs, so far as my personal experience goes, and this must now extend to at least 50 cases of so-called urticaria factitia, only in subjects in which the red line becomes surrounded by a visible erythema; it is also true that if this erythema develops, some degree of swelling can be predicted, almost confidently, before it appears, and that the brighter the erythema the more distinct in general is the wheal. In several striking instances in which whealing has from time to time been variable, I have noticed that on occasions upon which no wheal appeared, neither has the erythema, although the central red line has been seemingly of its accustomed brightness. The association between the two phenomena is so close that it has been commented upon repeatedly, and, as it can hardly be regarded as accidental, calls for explanation: however, a few exceptions to the general rule require notice. Thus, Ebbecke³ and Parrius¹⁰ both cite cases of whealing in which they were unable to detect any preliminary reddening or substantial reddening of the skin; apparently in these instances neither red line nor flush was visible. So far as the erythematous flush is concerned the only exceptions I have seen have been isolated cases showing flush and wheal on the trunk, and on the arms a diminutive wheal preceded by a red line only, or by a red line and a scarcely perceptible flush. In one such case, the only one so tested, a surrounding arteriolar flush could be detected if the stroke were put down on the previously cyanosed arm. The relation between a preliminary flush and œdema is emphatic in instances where urticaria is "spontaneous": as is well known, a circular or irregular patch of brightly flushed skin develops and a central wheal soon follows.

The relation between the arteriolar flush and œdema of the skin might be explained upon the following basis. A fully developed urticarial wheal projects sharply 2 or even more millimetres above the general skin level: the fluids contained in it may be taken for purposes of argument to double the thickness of the skin; the œdema is in the true skin, according to all those who, like Gilchrist⁵ and Hodara⁷, have cut sections of fresh wheals. This great increase of skin thickness, readily appreciated when a portion of the wheal is excised, can occur in the space of 3 minutes. We may take the normal supply of arterial blood to the whole arm when warm and resting

to be between 5 and 10 cc. per 100 cc. of tissue per minute (Hewlett⁶, Stewart¹³). The skin is not the most vascular part of the arm; but, if we allow that the flow to the skin is in the same proportion as to the arm as a whole, it would take some 10-20 minutes to double the skin volume assuming that the whole blood (corpuscles and plasma) flowing to it in its unstimulated state were retained there. If we allow, as we must, that the œdema fluid is drawn from the plasma of the blood and if we allow, further, that half the fluid entering the vessel passes through the walls, the corpuscles and some plasma passing on, then the flow required to produce a full wheal in 3 minutes would be 7 to 14 times the normal quantity.* Such a flow could not be obtained, a wheal could not form as fully and as quickly as it does, in the absence of arteriolar dilatation; arteriolar dilatation is essential. The rare instances of wheals developing without visible preliminary reddening of the skin do not negative this argument, for an increased blood supply to the skin is not necessarily associated with reddening; the last depends on dilatation of venules and capillaries; and this is not an inevitable result when the arterioles widen³. Thus, it seems clear that dilatation of the arterioles along the line that wheals is essential, and we require only evidence that the arteriolar flush (*b*) on the line is a part of the surrounding reflex flush (*c*). This evidence is not forthcoming, on the contrary there is evidence (to be described in Part II) that in the central line the arteriolar flush is of distinct origin; that being so, the reason why the surrounding flush and whealing are in general associated, must still remain unexplained.

Ebbecke in his article records new experiments with the object of showing that wheals may easily be produced in normal subjects; he leaves it to be inferred that wheals comparable to urticarial wheals are readily produced in normal skins by inducing a strong passive hyperæmia. His observations, if he has correctly interpreted them, would be of much importance, and must be considered in some detail. The end of a glass tube, a half centimetre in diameter and having rounded edges, is pressed heavily into the skin of the forearm; the skin inside the tube is greatly reddened, and small petechiæ may form in it. On lifting the tube a central wheal is found. This experiment described by Ebbecke is easy to repeat. The skin reddens inside the tube as he states; but on removing the tube, the chief effect is seen to be, not a wheal, but a ring-shaped and deep depression in the skin; in the centre of this is an island of skin, elevated about 2 mm. above its base. The depression in which it lies gives the impression that this skin is more swollen than it actually is. It often is swollen, but only slightly, its surface lying level with, or a fraction of a millimetre above, the level of the surrounding unaffected skin. If pressed upon or stretched in common

* In some more recent observations with Dr. Wolf, reported in a succeeding article, it is found that the temperature of the skin rises 1.5° to 2.5° C. during the development of a wheal (from an original temperature of about 32.5°). We calculate from separate data that such a rise of temperature means, at the least, a four-fold increase of blood flow.

with the surrounding skin, it becomes paler than does the latter, as is the case with a dermatographic wheal; this fact and the frequent slight elevation above its former level shows that the tissue fluids in it are increased. They are only slightly increased, and the explanation of this slight increase is perfectly simple. The heavy pressure of the glass ring on the skin forcibly drives out the fluids from the tissue spaces of the skin under the ring and the fluid passes into the neighbouring skin, which in part lies inside the tube and in part surrounds the tube. To produce the changes described a pressure equivalent to about 26 atmospheres* has to be exerted by the ring of glass on the skin, this pressure being maintained for about 60 seconds. When the tube is removed not only the skin inside the ring, but that outside is found to be lifted a little above the general level (Figs. 1 and 2). There is a slight wheal both inside and outside, the latter being less conspicuous because the fluid is more widely distributed; it is the central area of skin alone that is congested during the period of pressure, the outside area being rendered relatively anæmic by stretching. The production of the circular wheal is due almost entirely† to a simple mechanical transference of tissue fluid from one skin area to another; and the wheal is evidently quite distinct in form and causation from that known as "factitious urticaria." The amount of real swelling is not to be compared with that found in the last condition; the circular wheal at its height has neither the degree of pallor nor the translucency of a wheal produced by stroking; the first can be brought to its full height in 5 seconds, if the pressure exerted is very heavy, and it grows no higher if a lesser pressure is subsequently maintained for 2 minutes; that is so because all the available fluid in the skin under the ring has been pressed out quickly by the initial very heavy pressure. That the circular wheal has little or nothing to do with events in the capillaries is shown by the fact that it can be produced with equal ease on the skin of an arm, denuded of blood to a waxy pallor by means of an Esmarch's bandage: in this instance the skin inside the tube is not reddened during the period of pressure. Incidentally, it may be stated that these circular wheals are produced no more easily in those who show striking dermatographic wheals than they are in those who do not.

Effects of congesting the skin by suction. Ebbecke's first experiment leads to a second, which is equally important from our present point of view. It is stated that wheals may be produced when suction is applied by means of a small capsule. I have applied suction to the skin of a sufficiently large number of subjects to know that this experiment is also open to misinterpretation. If a glass tube 8 or 10 millimetres in internal diameter is employed, the result is very similar to that produced by pressure with the same tube, and

* About 7 lbs. weight is required on a glass tube of 1.32 inch thickness, and of 2.3 inch external circumference, or about 395 lbs. to the square inch.

† Some of the swelling will be due at first to congestion, and a very little to hæmorrhage into the tissue, when this occurs, but these minor factors may be neglected.

is mainly due to the same cause, for the skin in actual contact with the glass is stretched and pressed upon and the fluid of this ring of skin is displaced into the neighbouring skin within and without the tube. A more satisfactory plan is to use a capsule having a mouth of four or five centimetres diameter; for under these conditions any fluid displaced by the margin of the capsule to the skin within it does not bulk largely and the observations thus yield the more uncomplicated effects of lowered pressure. Suction is applied to the skin of forearm or back, and negative pressures ranging from 30 to 100 mm. Hg. are employed and maintained for periods of 2 to 5 minutes. On removing the capsule, the central reddened area of skin is surrounded by a circular trench, where the skin at the margin has been stretched against the glass edge (Fig. 3). Petechial hæmorrhages over the central area are usual with suction surpassing 70 mm. Hg., the critical pressure varying somewhat from subject to subject: but a wheal in the true sense is never provoked by this means, either in normal skins or in those which easily display factitious urticaria on stroking. There may be a very slight puffiness or elevation of the skin, but it has not lost its elasticity as it has when a true wheal is formed. Some of the slight temporary swelling is due to simple congestion, the skin remaining red for a while; a little swelling bordering the inner and outer edges of the glass is due to tissue fluid being expressed from the skin which is pressed against the margin of the capsule; some may be due to the transference of tissue fluids from deeper to more superficial tissues as a consequence of the suction; it is possible, indeed probable, that a very slight amount of fluid may be filtered out from the capillaries; if the last factor were wholly the cause of such swelling as exists, and it is not, the amount of this filtrate would bulk far less than would the fluids gathering during a similar period of time in a dermatographic wheal (Fig. 3). Moreover, the slight puffiness produced by a suction capsule subsides and is imperceptible within a few minutes. On many occasions I have used suction of this kind, covering a wide range of pressures (— 30 to — 100 mm. Hg.), on the skins of various patients who show urticaria readily on stroking, and have stroked the skin in the neighbourhood of the capsule at the same time that suction is applied inside the capsule. The suction is maintained until the wheal outside comes to its height (usually 3-5 minutes) or longer. The reddening of the skin within the capsule in this experiment when the suction is powerful is of a deeper hue at all stages than it is in the red line of the skin, the first reaction to the stroke; often several or hundreds of minute hæmorrhages develop over the area of suction, none develops where the skin has been stroked. When the capsule is removed, congestion and a little puffiness mark the site of suction, a conspicuous wheal, standing about 2 millimetres above the general level of the skin, marks the line of stroke (Fig. 3). Between the excess of fluid gathered in the two areas there is no comparison. If similar suction is applied to an arm which has first been depleted to a waxy pallor by means of an Esmarch's bandage, a very similar deformity of the skin is produced, though naturally it lacks the redness

of congestion and of petechial hæmorrhages. Urticarial wheals, as a reaction to stroking, never appear on an arm under similar conditions.

When suction of 100 mm. Hg. is applied to the skin surface a not very dissimilar fall of pressure must occur in the underlying tissue spaces: the pressure inside the small vessels will not change correspondingly, for blood is free to flow, and does flow, into them. The difference in pressure between the contents of the vessels and of the tissue spaces is forced much above the normal: for this reason the vessels distend. The degree of this distension and the exaggeration of the differential pressure may be gauged by the rupture of many minute superficial vessels. The degree of engorgement, judged by depth of colour and by these hæmorrhages, exceeds that occurring in the vascular reaction to a stroke put down at the same time and side by side on a skin susceptible to urticaria. The suction is maintained until a wheal has fully developed on the line of stroke; in the two instances a similar time elapses, yet at the end nothing approaching to a wheal is found on the area submitted to suction. The effects of less powerful suction are similar, though less in degree. It seems clear from such observations that neither an increase of differential pressure, nor distension of the vessels, is alone competent to create the œdema of a wheal. The conclusion that these factors play at the most a subsidiary part in the phenomenon is supported by the next observations.

Effect of venous congestion on a developing wheal. An armlet is placed on the upper arm of a patient susceptible to urticaria and pumped to the desired pressure; the veins of the forearm become engorged. The pressure is maintained for a number of minutes to be certain that full venous pressure is obtained and the congested arm is then stroked firmly. The time taken for the wheal to appear, and its state when fully developed, is noted and compared with observations on the control arm.

A large number of observations, which the accompanying Table I illustrates, establishes the fact that an increase of venous pressure neither expedites the appearance of the wheal nor exaggerates its prominence. On the contrary, the wheal is generally more prominent on the control than upon the congested arm; especially is this the case when great congestion (i.e., 70-100 mm. Hg.) is employed.

The smaller size of the wheal on the congested arm is not due to masking by slight general œdema of the tissues which might be supposed to develop. Thus, the right and left arms are stroked, the right arm having previously been congested by means of a pressure cuff at 70 mm. Hg. for 3 minutes. Three minutes after the strokes the wheal (*L 1*) on the left arm is more prominent than that (*R 1*) on the right arm. The cuff is now transferred to the left arm and this arm is similarly congested at the same pressure and for the same period. The two arms are again stroked (*R 2* and *L 2*). When the wheals have developed, that on the uncongested arm (*R 2*) is again found to be the more prominent; and on re-examining the first wheals (*L 1* and

TABLE I.

Blood pressures.	Arm congested.	Pressure		Wheel appears			Wheel most prominent on
		in mm. Hg.	applied in mm. before stroke	congested arm.	control arm.	Wheels compared at	
Subject 1. S. B. P. 135 D. B. P. 70	Right	30	2'	1' 20"	1' 50"	3' 0"	Slightly on congested arm.
	Right	50	2'	1' 40"	1' 50"	4' 30"	Slightly on control arm.
	Right	70	2' 30"	1' 20"	1' 30"	4' 0"	Almost equal.
	Left	30	2'	1' 30"	1' 60"	5' 0"	Equal.
	Left	50	2'	2' 0"	1' 40"	5' 0"	Slightly on control arm.
	Left	70	2'	2' 0"	1' 50"	5' 0"	Slightly on control arm.
Subject 1. (later date) S. B. P. 130 D. B. P. 65	Right	60	3'	1' 30"	1' 50"	4' 0"	Equal.
	Left	80	3'	1' 40"	1' 40"	4' 0"	Much more in control arm; pectechial at left elbow.
							Much more on control arm; pectechial at Right elbow.
	Right	100	3'	1' 50"	1' 50"	4' 0"	Equal.
Subject 2. S. B. P. 123 D. B. P. 92	Left	50	2'	2' 20"	2' 35"	7' 0"	Equal.
	Left	50	2'	2' 45"	2' 30"	—	
	Right	70	2'	1' 20"	1' 20"	3' 0"	Much more on control arm.
Subject 3. S. B. P. 108	Right	70	3'	1' 50"	1' 30"	3' 0"	Much more distinct on control arm; pectechial developed.
	Left	70	3'	1' 0"	1' 30"	3' 0"	Much more distinct on control arm. Stroke on left arm heavier than on right arm. Pectechial developed.

R 1) the original difference between these two is found to have been maintained. . If it were a question of masking by slight general oedema that would not be the case ; for the oedema of the left arm, now congested, should tend to mask the first wheal (*L* 1). As the four wheals are watched for a further period of 15 minutes, neither arm being meanwhile congested, the differences in size are maintained : that is to say, *L* 1 remains more prominent than *R* 1, *R* 2 remains more prominent than *L* 2 : yet both arms have been congested in equal amounts and for equal periods of time. Thus, congestion of an arm, upon which a wheal already stands, has no perceptible effect on the wheal, but a wheal forming on a congested arm does not develop fully.

The rise in venous pressure in the congested arm must raise to an approximately equal extent the pressure in the capillaries and venules : the degree to which these small vessels become engorged is witnessed to by the deep colouration of the skin and by the development oftentimes of groups of petechial hæmorrhages when heavy pressures have been employed. These hæmorrhages are usually to be seen when cuff pressures somewhat exceeding 70 mm. Hg. have been employed, first appearing in the loose skin of the ante-cubital fossa.* These experiments illustrate again the want of relation between the amount of the oedema formed and the distension of the vessels on the one hand and differential (vessel-tissues) pressure on the other.

The very decided effect of venous congestion (such as is produced by 70 to 100 mm. Hg. cuff pressure) in reducing the size of a developing wheal, is due to interference with the supply of blood to the skin. The effect of congestion at 30 mm. Hg.† are relatively slight, but as the degree of congestion is raised the effect increases ; it increases especially when pressures near the diastolic arterial pressure are used ; when pressures approaching closely to the systolic arterial pressure are employed there is no wheal. These findings are compatible with those of Stewart¹², who has shown that while congestion to half the diastolic pressure causes a relatively small diminution of blood flow to the hand, congestion to diastolic pressure very seriously diminishes the flow and that an armlet pressure 10 to 15 mm. below systolic pressure almost abolishes the flow.

Effect of obliterating the artery. Consistent with these results is the observation, repeated on a score or more of patients in the last eight years, that susceptible subjects never show a trace of whealing on the arm if the vessels of the limb are first completely occluded. In these circumstances the red line develops after stroking : the surrounding flush does not and no

* The liability of the minute vessels to break and cause petechial hæmorrhages is a question worth further investigation. Thus, recently, in a case of subacute infective endocarditis, a pressure of 60 mm. maintained for 3 minutes produced innumerable petechial. Such a reaction is not normal, and suggests that in this condition the vessels concerned are tender ; in this may lie the well known tendency of these cases to present spontaneous hæmorrhages into the skin.

† Cuff pressures much lower than 30 mm. Hg. cannot be used and accurately read in terms of pressure on the arm ; but that minor rises of venous pressure are not efficacious in increasing the size of the wheal is shown by stroking the arm, when the list is held at different levels, relative to the heart. It seems immaterial whether the arm is held horizontal or hangs vertically or lies in an intermediate position ; the wheals produced by stroking are alike.

wheel appears, even if occlusion is maintained for 10, 15 or even 20 minutes. This fact shows clearly, what might be anticipated, that œdema cannot form in the absence of vascular flow. It justifies us in the natural assumption that the œdema fluid is derived directly and wholly from the blood plasma.* In such observations the adequacy of the stroke on the occluded limb is shown by releasing the armlet several minutes† after a control wheel has appeared on the opposite limb. A wheel now develops rapidly over the original line of stroke. I have endeavoured to induce the wheel on an arm in which the circulation has been stopped, by massaging the blood in and out of the red line, but without success. A sufficient supply of blood apparently cannot be maintained by this means.

Effect of suction on a developing wheel. For the most part these observations have been undertaken on the skin of the back, where wheels develop most prominently. In the interscapular region a long firm stroke is made and a capsule is at once applied and the pressure reduced to —30 to —70 mm. Hg. over the middle third of the line. The suction is maintained

TABLE II.

Subject.	Region.	Pressure in mm. Hg.	Duration in mins.	Wheel begins outside.	On release.
1.	Back	— 50	2	1 min.	Wheel distinctly less within capsule area; the same 45 mins. later.
	Back	— 70	4	1 min.	Petechiæ formed. Wheel much less prominent, though broader, within capsule area; the same 35 mins. later.
	Back	— 110	3	soon	Wheel flatter but broader within capsule area. Hundreds of minute hæmorrhages.
2.	Back	— 50	3	1½ mins.	Same within and without.
3.	Back	— 80	4	2 mins.	Petechiæ formed. Less prominent but more diffuse within capsule area.

until the wheel above and below the capsule is fully developed; then the capsule is removed and the line examined in its length. Within the capsule, the wheel appears to develop almost as quickly as outside. On removing the capsule, the capsular portion of the wheel is almost always found to be reduced in prominence, though it may be broadened (Fig. 4). Occasionally this

* Ebbecke⁴ has shown that if Trypan red (or blue) is injected into the circulation, the dye appears in a wheel while it is forming, an observation which not only proves the origin of the fluid but evidences increased permeability of the minute vessel walls.

† If this interval is sufficiently prolonged, a wheel does not develop over the original line of stroking, a fact which will be discussed more fully in a subsequent communication.

portion of the wheal has the same appearance as the remainder ; it is never more prominent than that over the area which has not been submitted to a reduced external pressure. In the period during which the wheal is forming, the skin in the capsule is elevated by the suction and is of a purple colour ; this colour, when strong suction (70-100 mm.) is applied, is much deeper than that developed in the red line outside the capsule ; also, in this skin petechiæ often develop. This observation is consistent with other instances of congestion previously described, in that it fails to show an increased œdema when the distension of the minute vessels is increased. It is assumed that in the area beneath the capsule the full vascular reaction to the stroke is developed and preserved ; in addition to dilatation of capillaries and venules, the arterioles dilate ; the last may be shown by relaxing the suction, when the surrounding flush becomes visible ; the flush is present during the period of suction but is then masked by general engorgement. That the differential pressure between small vessels and tissue spaces is increased by the suction is unquestionable ; the effect of the suction upon the arterioles is open to more doubt. I know of no definite evidence that such suction will increase or decrease the amount of blood steadily flowing to the part. If it is decreased the reduced size of the wheal might be explained on this basis.* On the other hand, the meaning of this reaction may be found in dispersion of the œdema into the surrounding tissues, the wheal is flattened and at the same time broadened.

The foregoing observations show clearly that fluid does not pass from blood vessel to surrounding tissue, to form a wheal, as a simple consequence of capillary distension, a distension such as might in that case be supposed to increase the permeability of the vessel walls. They further negative the assumption that the fluids pass out owing to an increased differential pressure producing a quicker filtration. Neither can it be said that the conditions are satisfied, when such increased permeability, as may be supposed to result from distension, is combined with a large rise of differential pressure. Obviously a further factor is needed. Can it be said that this factor is purely such an increased blood flow to the part as has been shown to be necessary ? Briefly, is the increased differential pressure, acting upon a wall whose permeability is supposedly increased by stretching, sufficient to force through that wall fluid in quantity enough to produce a wheal, given that this fluid is supplied by the vessels in adequate quantity ? A reply to this question is returned, I think, by the concluding observations, and the possible influence exerted by distension and vascular pressure is reduced to narrower limits.

Pressure just required to prevent a wheal appearing. A heavy stroke is made from the point of the shoulder well down the upper arm. A pneumatic armlet is at once applied and the pressure exerted within 15 or 20 seconds

* Later observations with the thermopile show that the temperature of the skin submitted to suction may remain normal or may be a little but definitely reduced, the last indicating a decreased blood flow ; this is presumably due to the pressure of the capsule impeding the outflow through the veins.

on the lower half of the line of stroke. A chosen pressure is maintained in the armlet for usually 3 or 4 minutes, by which time a wheal has developed fully over the upper half of the stroke and outside the armlet. The armlet is quickly removed and the skin under it at once examined. According to the pressure used, a wheal may or may not have developed. If a wheal is not present on removing the armlet it always develops fully and quickly after removing the armlet, thus showing the stroke to have been an effective stimulus throughout its length. The following table (Table III) illustrates these observations in three subjects, and shows that a pressure of over 30, 40, or even 50. millimetres of Hg. on the skin is necessary to prevent a wheal appearing, and that, up to these pressures, fluid is able to collect in the tissues to form a wheal (Fig. 5).

These observations have been confirmed and amplified in the following manner. Immediately after stroking the skin of the upper arm or interscapular region, a glass capsule is applied to a portion of the line and the pressure within it raised at once to a desired point and maintained. The events inside and outside the capsule are then watched. A protocol of a single series of observations will illustrate the method.

Subject 4. Syst. B.P.=115; Diast. B.P. 85.

(1) R. upper arm is stroked and capsule applied at 30 mm. Hg. over centre of line stroked. Outside, a bright red line, surrounding flush and prominent urticaria are developed during 3 minutes' observation. Inside the capsule a faint red line alone develops. On removing the capsule a very slight edema is found along the line of stroke beneath it.

(2) Repeated on L. upper arm; capsule applied at 30 mm. and stroke heavier. Appearances outside capsule as before. Inside capsule a slight red line develops, though not nearly so brightly as outside. After 4 minutes this red line is found to be obliterated if the capsule pressure is raised to 70 mm.. Removing the capsule, a very slight wheal is found, which quickly develops to a full wheal.

(3) Repeated on L. shoulder; capsule applied at 40 mm.. A vivid red line appears at 15 seconds outside; at 30 seconds a very faint red line appears inside, and this has brightened as outside. At 3 minutes, a full wheal is present outside, but on removing the capsule none can be found inside.

(4) Repeated on L. shoulder; capsule applied at 22 mm.. A red line is present inside and outside at 40 seconds; by the end of 1 minute its intensity is almost uniform throughout its length. The surrounding skin inside the capsule is flushed at 2½ minutes; the last has not been seen in previous observations, and a wheal is seen inside also at 4 minutes; the whole skin inside is whitened by raising capsule pressure to 60 mm.; a pressure of 50 mm. abolishes the flush, but the red line still remains very faintly visible. On removing the capsule at 4 minutes, there seems to be little difference in the wheal inside and out. The flush around the wheal requires 50 mm. pressure to abolish it when the capsule is re-applied.

(5) Interscapular region stroked and capsule applied at 35 mm.. At 30 seconds the red line is vivid outside and faintly seen inside. Flush well developed outside by 1 minute, it appears inside faintly at 1½ minutes. Wheal perceptible outside at 1½ minutes, but not inside. At 2 minutes the red line inside has become more distinct, though far less vivid than outside. At this stage a rise of pressure to 60 mm. abolishes the flush inside and renders the red line only just perceptible. At 4 minutes the wheal outside is full; on removing capsule a slight wheal is found beneath it, and this quickly develops to the full.

(6) Repeated at 40 mm. pressure. Same events outside. Inside the skin is uniformly pale at end of 3 minutes; at 4 minutes the capsule is removed and no wheal is found beneath it; a flush develops over the whole area compressed, and within a few seconds a wheal begins to develop along the line of stroke; it is equally developed with outside wheal in 45 seconds after capsule is removed. The flush now requires 55 mm. pressure to abolish it.

(7) Repeated at 35 mm. pressure. A slight red line develops inside at 20 seconds, and has brightened by 1 minute. A very slight flush inside at 1½ minutes. The flush requires 55 mm. pressure to abolish it, the red line rather more. At 4 minutes, the capsule being removed, no wheal is perceptible on this skin, but is fully developed outside. The inside wheal now quickly develops, as usual.

TABLE III.

Blood pressure.	Arm.	Press. in armlet,*	Press. maintained for	Upper wheal appears after stroke in	Upper wheal full at	Lower wheal.	Approximate pressure just required.
Subject 1. S.R.P. 135 D.R.P. 70	Left	70	3' 0"	—	—	Absent	40+
	Left	40	4' 0"	—	—	Slight	
	Left	40	5' 0"	—	—	Slight	
Subject 1. (later date)	Left	50	3' 0"	1' 35"	3' 0"	Absent	40+
	Left	35	3' 0"	1' 35"	3' 0"	Almost full	
	Right	40	3' 0"	1' 40"	2' 45"	Just palpable	
Subject 2. S.R.P. 123 D.R.P. 92	Right	40	4' 0"	2' 30"	3' 40"	Fully developed†	50+
	Right	50	5' 0"	2' 45"	1' 30"	Slight but distinct	
	Left	60	5' 0"	2' 25"	4' 20"	Absent	
Subject 3. S.R.P. 108 D.R.P. 54	Left	40	4' 0"	1' 15"	3' 0"	Absent	32+
	Left	32	4' 0"	1' 20"	3' 0"	Distinct but not full	
	Right	33	5' 0"	1' 15"	3' 0"	Just palpable	
Subject 3. (later date)	Right	30	5' 0"	1' 10"	—	Slight	33+
	Left	30	4' 0"	—	—	Well developed	
	Left	40	4' 0"	1' 15"	—	No wheal	
Subject 3. (later date)	Left	30	4' 0"	—	—	Absent	22+
	Right	30	4' 0"	—	—	Absent	
	Right	22	3' 0"	—	—	Slight	

* These pressures accurately express the pressures on the arm, at all events up to 90 or 100 mm. Hg, as could readily be shown by placing a small rubber balloon on the arm, connecting this to another manometer and covering it with the pneumatic armlet. As the pressures were raised in the armlet, the pressures recorded in the bag rose by the same increments; there was, however, a falling away of the pressure recorded in the balloon, as an armlet pressure of 90 or 100 mm. Hg. was surpassed. See also the observations cited from the same point of view in the previous communication.

† Flush develops round wheal after removal of armlet. Noted on these occasions.

These observations and similar series, each repeated, upon two other patients are briefly summarised in Table IV. They confirm the previous observations that urticaria will develop against pressures ranging from 30 to 50 mm. Hg.. They show, further, that when the pressure is just sufficient to prevent urticaria developing, a flush around the line of stroke is prevented in most instances or may appear only faintly, and that a visible red line is either developed faintly or may on occasion be suppressed. In other words, a pressure just sufficient to prevent urticaria developing is just sufficient to prevent the appearance of the preceding vascular reaction or, more

TABLE IV.
Events under positive pressure capsule.

Subject.	Skin tested.	Approximate pressures needed to prevent development of			Pressures needed to abolish a developed		Blood pressure.	
		red line.	flush.	urticaria.	red line	flush.	syst.	diast.
1.	Arm	85		55			154	76
2.	Arm and back	50+ to 60+	50+ to 60+	48	70-90	60-75	116	82
3.	Arm and back	45-50	30-35	40	about 90	50-60	120	70
4.	Arm and back	40	40	35-40	60-70	50-60	115	85

usually, manifestly to reduce it. In this relative anæmia of the stroked skin evidently lies the reason why pressures of 30-50 mm. Hg. suffice to prevent urticaria developing. Important conclusions are to be drawn from these observations, especially from those in which the pressure just preventing urticaria is almost or quite sufficient to abolish the preceding dilatation of the vessels.* These show that the increased pressure developed in the vessels, in response to the stroke, is counteracted in some instances completely or almost completely, by the capsular pressure in question. A slightly lower capsular pressure permits fluid to pass out of the vessels; here the distension of the vessels is small and the differential (vessel to tissue) pressure cannot greatly exceed the differential pressure of the surrounding unaffected skin.

* It may be asked, perhaps, why these observations are not carried out microscopically. To attempt to do so would greatly increase the technical difficulties, owing to the short space of time during which observation is possible. Moreover, I much question if the microscopic method, could it be carried out successfully, would present any material advantage. It might decide between a slight distension of the vessels and no distension, a trivial point. It could also decide the question of capillary as opposed to venule distension. The point is this, it might be argued that the fluid passes out by the capillaries and not by the minute venules, so-called, and that the pressures employed were sufficient to prevent the last filling, but not the first, the last being mainly responsible for skin colour in the arm. The reply to this is two-fold. Firstly, if the venules are closed, there is no outlet for the capillary blood, and therefore no flow in them. Secondly, the similarity of structure between capillaries and minute venules and the depth to which the oedema is found to penetrate in sections, renders it hardly conceivable that the capillaries of the papillæ are alone responsible for the exudate.

It is here to be remarked that the pressure needed to prevent the appearance of the red line, and the pressure needed to abolish such a line once it has developed, does not seem to differ materially in the case of those prone or in those not prone to wheal, given that such control subjects are chosen for comparison who give rather vivid red lines on stroking. The absence of material distension of the vessels in many of these observations, in which there is developed an œdema, reduced in amount it is true but present nevertheless, may be coupled with the observations in which wheals have been seen to follow strokes yielding little or no visible reddening of the skin.* The evidence, presented by the pressures determined, suggests most strongly that filtration under an enhanced pressure may be disregarded; it certainly places any hypothesis of simple filtration through normal capillaries finally out of court. For if pressures of as much as 70 or more mm. Hg. are sometimes developed in the minute vessels of the skin without œdema developing, as they are in red lines produced in normal skins by stroking, pressures exceeding these by 40 or 50 mm. at least would be required when œdema develops in urticarial skins under our capsule. The full values would then approach or surpass the normal systolic blood pressures, which are often on the low side of normality in urticarial patients. The same observations and the conclusions drawn from them, while disposing of the view that a sufficient increase of permeability can result from simple stretching of the endothelial walls, at the same time convince us not only that increased permeability occurs, but that it occurs in a remarkable degree. When a diminutive wheal develops under a pressure capsule, it is diminutive because the outside pressure checks the rate of blood flow in the affected vessels: it is possible in these circumstances that increased permeability is the sole change determining the œdema. Under the more natural conditions at which full wheals develop, increased permeability does not suffice, it must be associated with greatly increased blood flow.

Further to evidence the increased permeability of the capillary walls the protein content of the wheal fluid may be cited. The percentage content is difficult to ascertain accurately owing to the small amounts of fluid available. If several capillary glass tubes are driven into a fully developed wheal, and gentle pressure is exerted on the wheal, it is possible to collect 4 or 6 tenths of a cubic millimetre of clear fluid. This quantity, drawn from one of our patients (Subject 1) was diluted exactly 10 times in graduated fine-bore tubing, taken up into tubing of 1.5 mm. bore and mixed with an equal quantity of absolute alcohol. At the same time an equal quantity of the patient's blood serum, diluted 8, 10, 12, 15, 18 and 20 times, was treated similarly. The tubes were sealed and the precipitates examined before and after centrifugalising. The precipitate in the wheal fluid tube

* Parrissin² himself concludes from the very full urticarial wheal produced in his patient in the absence of a substantial reddening of the skin, that increased permeability of the capillaries consequent on their over-distension, could not have been responsible for the urticaria.

was judged, both before and after centrifugalising it, to correspond to that of the serum 15 times diluted. In another observation (on Subject 2) the protein in the wheal fluid, 10 times diluted, corresponded to that in serum from a normal subject diluted 12 times. Thus the protein-content of the wheal fluid approximates much more closely to that of the blood serum than does the protein content of lymph from the limbs (see Starling¹¹). The wheal fluid forms perfectly distinct clots of fibrin, in which a few leucocytes are enmeshed, soon after it is withdrawn; the flakes of fibrin found in two-tenths of a cubic millimetre of fluid are sufficiently large to be seen with the naked eye. They have been removed before the fluid has been used for protein estimations.

A final observation confirms the general argument that the simple effects of vascular dilatation, even when accompanied by increased blood flow, do not stand alone or together as the sole causes of the wheal, and points therefore to increased permeability of the vessel walls as the dominant factor. If suction is applied to the region of flush surrounding the preliminary red line of the developing wheal a dilatation of the minute vessels controllable in its degree is added over an area in which the arterioles are already appropriately dilated, and thus all the recognised and simple vascular conditions would appear to be fulfilled. Yet no trace of wheal develops where this suction is applied. What is lacking is that the skin so tested has not been stroked, and the endothelial wall of the minute vessels has not been altered to that degree of increased permeability, which the stroke seemingly engenders, and which is requisite for the rapid outpouring of fluid.

It is perhaps expedient to state that the conclusions now drawn are intended to apply solely to the form of œdema discussed; further observations may show that they are or are not relevant to other varieties of œdema, but whether that may prove to be the case or not, strictly limited conclusions are obviously desirable in the present state of our knowledge.

CONCLUSIONS.

1. The skin of all young subjects wheals when suitable stimuli are applied, though the susceptibility of the skin, as measured by the strength or number of stimuli applied, is variable. Dermatographic wheals result from purely physiological processes.

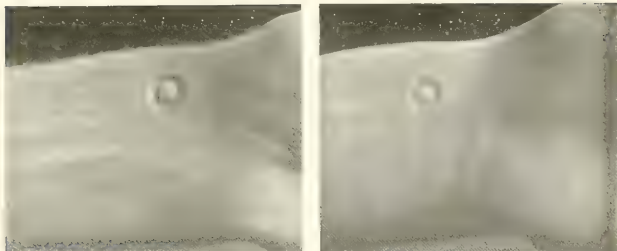
2. The pressure at which the wheal-fluid is able to collect in the tissues amounts to 30-50 mm. Hg.. It clots on standing and subsequently its protein content is found to be 67 to 84 per cent. that of blood serum.

3. The œdema, which goes to form the dermatographic wheal, is independent of such increased permeability of the vessel walls as may be supposed to follow simply from their distension; it is independent of

though it may very probably be aided by an increased filtration pressure. It is due essentially to increased permeability of the vessel wall, consequent upon the stimulus but arising in a fashion at present unknown, and the rate at which the fluid is delivered to the tissue spaces is controlled mainly by the rate at which blood flows through the damaged vessels.

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Figs. 1 and 2. Examples showing the results of pressing the end of a thick walled glass tube heavily into the skin of the normal arm. The pressure leaves the skin depressed; the tissue fluids have been forced to the centre and to the sides, producing an oedematous circular patch of skin and a little rampart of oedema bounding the outside of the trench.



Fig. 3. *Subject 3.* The skin of the back has been stroked vertically, and at the same time a suction capsule has been applied to the skin at a pressure of -90 mm. Hg.. At the end of 4 minutes the capsule was removed and the photograph taken. The stroke has produced a full wheal. The margin of the suction capsule has depressed the skin, and has induced a trifling puffiness of the central skin.

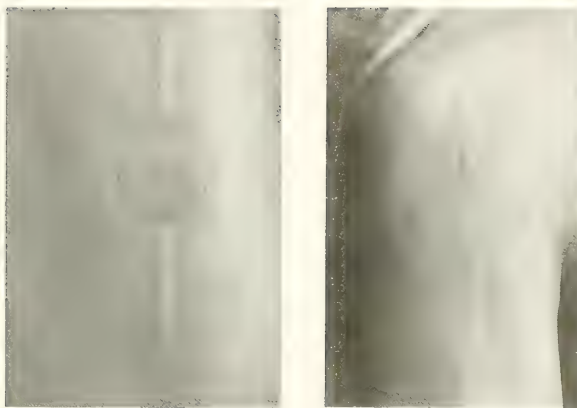


Fig. 4. *Subject 3.* The skin has been stroked and a suction capsule at once applied at 70 mm. Hg. over its centre. At the end of 3 minutes the capsule was removed and the photograph taken. Outside the capsule area a full wheal has risen; where the margin of the capsule has pressed against the skin there is no wheal. Inside the capsule the wheal is greatly reduced in height but is diffused and increased in breadth.

Fig. 5. *Subject 3.* The skin has been stroked and a pressure capsule at once applied at 40 mm. Hg. The capsule was removed at the end of 4 minutes, and the photograph immediately taken. It shows a full wheal above and below the area of pressure and a slight but perfectly distinct elevation of the skin over the line of stroke within the area of the capsule.

THE INFLUENCE OF ALCOHOL ON THE ISOLATED MAMMALIAN HEART.

By R. SULZER.

(With an appendix on "The estimation of alcohol in blood," by
R. K. CANNAN and R. SULZER.)

(*From the Institute of Physiology, University College, London.*)

MANY researches have been made with a view to ascertaining the action of alcohol on the heart, but the conclusions arrived at are very contradictory. Their value is further reduced by the fact that in many cases perfusion fluids other than blood were used, or that the doses of alcohol were so great as to raise the concentration in blood to a level that never occurs when alcohol is taken by the mouth. None of those who worked on the influence of alcohol on the heart seems to have estimated the amount of alcohol in the blood by chemical means, and this might account for many divergencies in their results.

Thus Martin², working with his heart-lung preparation, found alcohol in dilution of 0.25% by volume (0.2% by weight) to dilate the heart, and in higher concentrations to reduce the output, whereas Kochmann⁵, when using Bock and Hering's method, observed the first effect of alcohol in concentrations of 0.8%, but with Langendorff's method of heart isolation he found the same effect with 0.4% alcohol. The action of alcohol, according to him, is to reduce the diastole as well as the systole and to diminish the height of the pulse. Loeb⁶, on the other hand, working with Langendorff's apparatus, comes to the conclusion that in concentrations of 0.13 to 0.3% alcohol has a stimulating effect on the mammalian heart and that there is no toxic influence below 1.0%. The results of Loeb as regards the stimulating effect of small doses were confirmed by Bachem¹, who used Bock and Hering's method for his experiments. Dixon³ also found an improvement in the heart beat and an increase in rate with small doses of alcohol, which he ascribes to the nutritive action of this substance, but in greater amounts than 0.5% he observed a diminution in the efficiency of the heart. As to the reaction of the coronary circulation to perfusion with blood containing alcohol, we find in the same paper the statement that the coronary vessels behave in the same manner as the vessels of other isolated organs, *i.e.*, that 0.1 to 0.2% alcohol causes a very slight dilatation, whereas with about 1.0 to 2.0%

alcohol in the blood constriction first ensues followed later by dilatation. According to Loeb⁶, however, alcohol does not influence the coronary circulation below 4.0%.

Equally divergent are the deductions made as to the action of alcohol on the heart muscle from observations on the reactions of the whole animal when this substance is administered by the mouth or injected intravenously.

It is evident that the question must be tested, as in the works already quoted, on the heart separated from the central nervous system, as well as from the action of chemical stimulants such as adrenalin. But—and this is a point not observed in most of the previous investigations—the action of alcohol must be tested on a heart which is performing a normal amount of work, and in which it is possible to keep all the factors which influence the work of the heart, namely, the arterial resistance, the inflow of blood, the temperature of the heart, and the rate of its beat, constant, apart from any possible influence of alcohol. These conditions are fulfilled only by the heart-lung preparation where all these factors are under the control of the experimenter, and the heart may go on beating regularly for hours, at a steady rhythm, sending out the same amount of blood at each stroke, and maintaining a constant arterial pressure. In such a heart, as has been pointed out (Patterson, Piper and Starling)⁹ any increase in the resistance it has to overcome causes increased diastolic and systolic volume of the ventricles, provided that the inflow is maintained unaltered. The mechanism by which the heart reacts to increased resistance to its contraction is by increased dilatation, the strength of the contraction being a function of the diastolic volume. Conversely, if the resistance and the venous inflow be maintained constant, any diminution in the functional capacity of the heart muscle means that the heart has to start from a greater diastolic volume in order to maintain the same output and pressure as it did with a higher functional capacity. The heart-lung preparation thus forms the best possible object, as Magnus has recognised², for determining the immediate effect of any drug or drug like substance on the functional capacity of the ventricular muscle, a tonic or improving effect of the drug being revealed by a smaller heart volume, while a depression of the functional capacity will be shown by the heart taking up increased diastolic and systolic volumes. To alcohol have been ascribed stimulant and depressor effects on the heart muscle. If it is a stimulant, addition of small quantities of this substance to the circulating blood, while all the other mechanical conditions of the preparation are maintained constant, should cause a diminution in the volume of the heart, both in diastole and systole, as is said to be the case for *strophanthus*². On the other hand, a depressant effect would be shown by increased dilatation of the ventricles, the dilatation affecting both diastole and systole. A still further depressor effect would be marked by a rise of pressure both in the left auricle and in the right auricle and by a certain diminution in the output of the left ventricle at each contraction.

Method.

The experiments were made on dogs anaesthetised with chloralose. As an index of the changes in heart action the arterial, venous and pulmonary pressures were recorded simultaneously. For this purpose the side tube of the cannula inserted into the innominate artery was connected with a mercury manometer, the excursions of which were recorded on a kymograph. Two other cannulae, one of which was introduced into the right auricle through the inferior vena cava, the other into the left auricle through the corresponding appendix, were each connected to water manometers. The cannulae, as well as the rubber connections, were filled with saline. The opposite limb of these manometers communicated each with a piston recorder which wrote the changes in water level on the kymograph. The changes in volume of the heart were taken by enclosing it in a Henderson cardiometer, connected with a large Palmer piston recorder, and the output of the heart was determined by measuring the time necessary to collect 50 or 100 cc. in a cylinder.

In a second series of experiments the changes in the coronary flow produced by alcohol were investigated by means of the cannula devised by Morawitz. According to Evans and Starling⁴ and Markwalder and Starling⁵, approximately three-fifths of the blood supplying the heart muscle can be obtained from the coronary sinus by means of a cannula introduced into it. The coronary output was taken at intervals by measuring the time in which 20 cc. of blood escaped through the cannula. The output per minute multiplied by $\frac{5}{3}$ then gives the total coronary flow per minute. In these experiments the arterial and venous pressures only were recorded.

The alcohol, 10% by volume in 0.9% saline, was added from a pipette to the blood in the reservoir from which the right auricle was supplied. Samples of about 10 cc. of blood were taken, the first before any alcohol was added, one after the maximum effect of each dose of alcohol was reached, and another generally five to ten minutes later. The amount of alcohol in the blood was estimated by the method devised by Cannon and Sulzer (see Appendix). The estimations of some of the samples were made on the same day, others were kept on ice overnight and analysed on the following day. The results of the estimations are given in per cent. alcohol by weight.

Results.

The action of alcohol on the heart muscle. The effect invariably observed after a sufficient dose of alcohol is a rise of the cardiometer curve, *i.e.*, dilatation of the two ventricles. This increase in volume of the heart is due to incomplete emptying at each systole and to an increased filling of the ventricles during the following diastole. At the same time the venous and pulmonary pressures show a slight rise. The dilatation of the heart can be observed with concentrations below 0.1% and reaches a considerable

extent with higher concentrations of alcohol. The pericardium was removed which otherwise would limit the dilatation. Thus in Fig. 1 *b* there is a slight but distinct rise of the cardiometer curve as compared with Fig. 1 *a* at a concentration of 0.06%, whereas in Fig. 2 we find with 0.8% an enormous

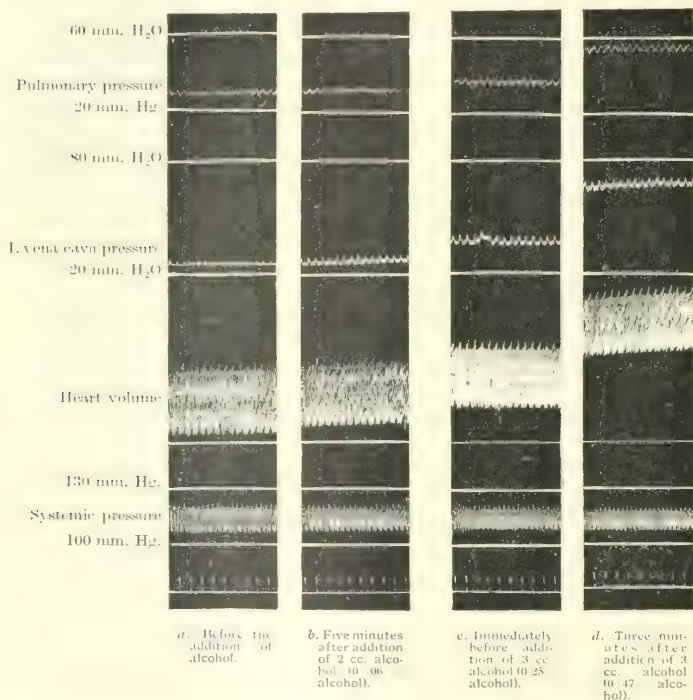


Fig. 1. *Experiment 4*, November 13th, 1923. Dog 7.25 kg. Anaesthetic: chloralose 0.72 gm., heart-lung preparation.

further dilatation of the heart already dilated from the previous additions of alcohol. On increasing the amount of alcohol in the blood, the output of the heart, as measured directly, begins to diminish, and the heart beat, as measured by the amplitude of the cardiometer curve, decreases. In consequence a further marked rise of pressure occurs in both the pulmonary veins as well as in the venæ cavæ, and is due to the ventricles being unable

to send out all the blood they receive by the corresponding veins. The output showed an appreciable decrease, generally between 0.3 to 0.4% alcohol, but in *Experiment 7* (see Table), which is somewhat remarkable in this respect, the output remained constant, although the alcohol in the

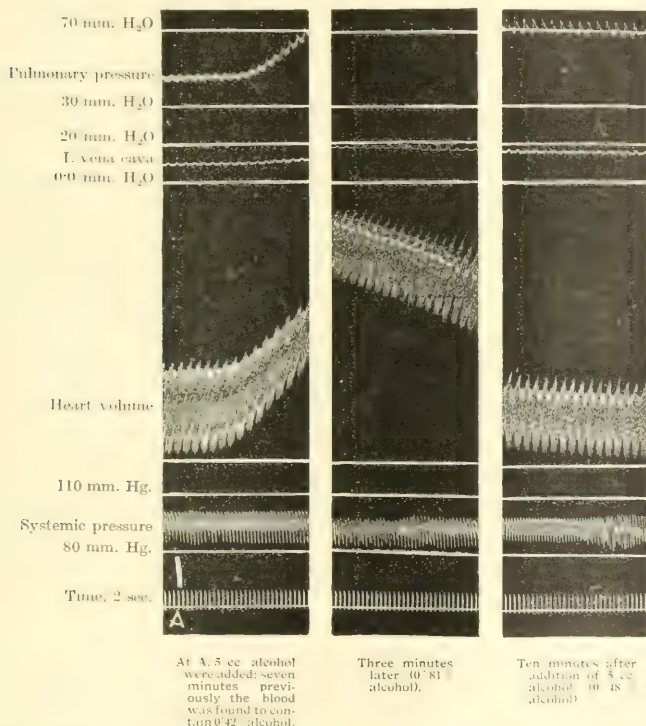


Fig. 2. *Experiment 2*, November 1st, 1923. Dog 7.15 kg. Anæsthetic: chloralose 0.71 gm.: heart-lung preparation.

blood reached 0.49%, while in another case it was found to be diminished at 0.2%.

The arterial pressure was only very little affected in these experiments. The fall of arterial blood pressure, if there was any, amounted only to a few mm. Hg.. A corresponding change of the heart's action in an animal with

intact circulatory system would have produced a considerable fall of pressure if there were no complicating action of alcohol on the blood vessels. The constancy of arterial pressure in these experiments is simply due to the construction of the peripheral valve like resistance employed in the heart-lung preparation, which is specially designed to maintain the blood pressure as constant as possible in spite of the variations in the output of the left ventricle.

The time-relations of the changes described vary widely with the time taken for the addition of the dose of alcohol. If the addition is made suddenly as in Fig. 2, the cardiometer curve, as well as the pulmonary and vena cava pressures, rise about 30 seconds after the addition, reach their maximum height from 2 to 3 minutes after the addition, and then begin to fall at a considerable rate. This surprisingly quick recovery is not observed when the dose of alcohol is added slowly within one or two minutes. In this case the curves rise towards the end of the addition of alcohol, and continue to rise for 6 to 12 minutes and then become constant. The recovery observed in some cases was only slight and very gradual. It seems, therefore, that the sharp rise and immediate fall of the curves in the case when alcohol is added suddenly is due to this substance reaching the heart at first in high concentration but getting more and more dilute as it becomes equally distributed in the whole of the blood in the system and in the tissues of the heart and lungs. This assumption is confirmed by the estimations of alcohol in the blood at the point when the maximum effect is reached and after recovery.

The condition of the heart under alcohol is therefore the same as occurs in fatigue, in so far that in both these circumstances it dilates more than an unaffected heart would do when performing the same amount of work. It is evident from this that the power of the heart to adapt itself to more work suffers under the influence of alcohol. I have obtained no evidence of any stimulating or improving effect of alcohol, even in small doses, on the heart muscle. As soon as any effect was observed at all, it was in the direction of diminished functional capacity.

Effects of alcohol on the coronary circulation. In our experiments the coronary flow always showed a decrease after adding alcohol to the blood, which became perceptible with 0.1 to 0.2%₀. In *Experiment 7*, for instance (see Table), the coronary flow diminished from 72 to 60 cc. per second with 0.2%₀ alcohol but rose again and reached the original height of 72 cc. after 13 minutes. In the same way after the second addition of alcohol the coronary flow came back to 72 cc. per minute after a fall to 65 cc.. Other experiments showed a decrease in flow of the same nature. As to the interpretation of these results, the constancy of the arterial blood pressure in the heart-lung preparation proved to be of great advantage. It permits us to exclude any change of pressure as the cause and suggests a direct constricting influence of alcohol on the coronary vessels.

Time.	Temp. °C.	Art. pressure. mm. Hg.	Inf. vena cava pressure. mm. H ₂ O.	System output cc. per min.	Coronary sinus output per min.	Coronary flow. Calculated c.c. per min.	Alcohol % in blood.	Addition of
12.05	35.5	99	34	500	43	72	0.13	
12.08	35.0							3 cc. alcohol.
12.10	35.0	97	35		36	60	0.21	
12.12	35.5	98	34	500	37	62		
12.21	35.5	98	30	500	43	72		
12.25	35.5							5 cc. alcohol.
12.28	35.5	97	38	500	40	67	0.49	
12.32	35.5	97	41		39	65		
12.39	35.7	98	39					
12.45	35.7	97	37	500	43	72	0.48	

Experiment 7, November 23rd, 1923. Dog 9.5 kg. Anesthetic: chloralose 0.95 gm.; heart-lung preparation. Cannula in coronary vein.

The concentration of alcohol in blood was also calculated after estimating the amount of blood in the system. The figures thus obtained were always higher and on an average 39% above the value found by direct chemical analysis. The difference is probably due to the tissues of the heart and lungs taking up some part of the alcohol, and it might be significant in this respect that Kochmann⁵ found a lower concentration to be active when using Langendorff's apparatus than in his experiments with Bock and Hering's method, where the heart remains in the thoracic cavity and the circulation through the lungs is left intact. This is not to be understood as indicating elimination of alcohol by the lungs, but to these organs taking up some part of the alcohol. Although elimination of alcohol through the lungs undoubtedly takes place, this process seems to be so slow that it could not account for the difference in the active concentration observed by Kochmann with the two methods.

Dixon³, in his paper on the action of alcohol, ascribes the rise in blood pressure, which he, like other workers, observed after small doses of alcohol, to an increased efficiency of the heart. My experiments never showed anything which might be explained by an improvement of the heart's action. Even if we assume that alcohol can act as a source of energy to the heart muscle, this action would not produce any effect on the beat of a heart supplied with blood, as this already contains a sufficient amount of foodstuffs. It is therefore concluded that the rise in blood pressure observed after small doses of alcohol (even if such small doses have any direct influence on the heart) cannot be due to, but occur in spite of, the action of alcohol on the heart.

These experiments thus confirm and extend the observations made as long as forty years ago by Martin⁸, who certainly worked with more primitive methods that are at present at our disposal. As his paper on the action of ethyl alcohol on the dog's heart is to be found in a few science libraries only, the most important passage from this work is quoted here.

"The action of alcohol administered in the manner and doses above described is, without primarily altering the force of the heart beat, to alter its character, so that the ventricular cavity is not obliterated at the end of systole and less so the longer the alcohol has been administered. At first this incomplete systole is compensated for by a more extensive diastole, so that the difference between the capacity of the ventricle in complete diastole, and that in complete systole remains the same as when the organ was normally beating. Consequently, the quantity of blood pumped out at each beat remains as great as before. If the heart be confined in the pericardium it soon, however, ceases to have room to swell during diastole to a size sufficient to compensate for its incomplete systole: and thenceforth, as the swelling increases the difference between systolic and diastolic capacity becomes less and less. As the necessary result, the quantity of blood pumped round by the organ is proportionally diminished. Removal of the pericardium prevents this result, at least for a considerable time." A remarkable anticipation of the results of more recent work.

APPENDIX.—THE ESTIMATION OF ALCOHOL IN BLOOD.

BY R. KEITH CANNAN (BEIT MEMORIAL RESEARCH FELLOW) AND R. SULZER.

The method for the estimation of alcohol in blood which appears to have achieved most favour is that of Pringsheim¹².

A weighed amount of blood is distilled under reduced pressure, the distillate condensed by ice-cold water is treated with a measured volume of standard potassium dichromate in acid solution at 100°C. for one hour in a closely stoppered bottle, and the unreduced potassium dichromate is titrated with standard ferrous ammonium sulphate. We found the method troublesome and tedious. Distillation of such a fluid as blood involves much frothing and requires constant control, whilst the titration demands the use of an outside indicator whose end-point only becomes precise with experience. The method, again, is not adaptable to very small amounts of alcohol.

The method that we have employed relies on the same principles, but a modification of apparatus and technique has yielded a considerable economy of time and an iodometric titration has made possible the determination of very small amounts of alcohol.

Method. A known volume of blood is delivered directly on to two or three times its weight of anhydrous sodium sulphate, which is distributed over the bottom of the distilling vessels. This is placed in a water bath at 40-50°C, and evacuated through a tube containing a known volume of standard potassium dichromate and an equal volume of strong sulphuric acid (the nitrogen free sulphuric acid, B.D.H., was found satisfactory as it contained an inappreciable amount of oxidisable matter). The distillation is allowed to proceed for 15-25 minutes with the pump running, the vacuum is then broken by opening the capillary inlet of the distilling flask and the absorption tube disconnected. The contents are washed into a flask with sufficient water to dilute the sulphuric acid to less than 5%, excess of 10% potassium iodide solution is added and the liberated iodine titrated with standard sodium thiosulphate and starch in the usual way. This titration subtracted from the thiosulphate titre of the volume of potassium dichromate used gives the amount of the latter required to oxidise the alcohol, and from the factor $(\text{Icc. N})/10\text{K}_2\text{Cr}_2\text{O}_7 = 1.15$ mgms. alcohol) the amount of alcohol may be directly obtained.

Remarks. The amount of anhydrous sodium sulphate used should be such as to give a semi-liquid mass with the blood. Complete drying of the blood by excess of salt might involve some retention of alcohol. Using this anti-frothing device distillation is facilitated and the volume

of the distilling vessel may, in the case of 5 cc. of blood, be safely reduced to 100-200 cc.. "Pure dry sodium sulphate" may be used with confidence. The principle that 50% sulphuric acid completely absorbs alcohol, and, with the simultaneously presence of potassium dichromate, oxidises it almost instantaneously to acetic acid, explains its complete retention even in a vacuum. This is emphasised when one notes that a dilute solution of alcohol may be estimated by direct addition from a pipette to such an oxidising mixture even if it be at a temperature above the boiling point of alcohol.

Since the adoption of this method it has been found that such oxidising mixtures have been in use for many years in some industrial laboratories for the determination of alcoholic liquors! For this reason it would not appear to be necessary to do more than say that each step in our method has been carefully controlled and found satisfactory. It is to be noted, however, that it is necessary that the strong sulphuric acid be added to the potassium dichromate slowly and with careful cooling, as otherwise the heat of reaction may result in reduction of a small proportion of the latter to the chromium salt. As a further check we have always standardised the thio-sulphate solution against dichromate solution which has been mixed with acid in the above manner and then diluted to a concentration of 5% of sulphuric acid.

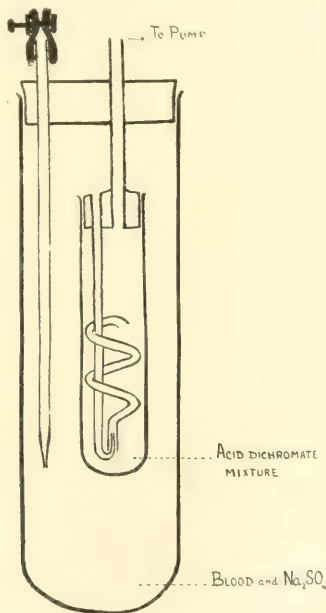


Fig. 3.

In the diagram (Fig. 3) is represented a self-contained system of distilling bulb and absorption tube designed for ease of manipulation and economy of time and space. The loose-fitting spiral eliminates splashing of the viscous oxidising mixture during evacuation—a requirement necessitated by a reduction to the minimum of the volume of the absorption bulb.

The values obtained for the "alcohol" of fresh human and dog's blood by this method have been of the same order as those recorded in the literature¹¹, namely, 2.5 — 4 mgms. per cent. It may be remarked that these values for what we prefer to call the "volatile carbon" of the blood

are only slightly greater than would be given if it consisted only of the volatile ketones (acetone), whose concentration has been frequently determined.

It is believed that the method described provides a rapid method for the estimation of alcohol in biological fluids generally, in which the presence of other volatile oxidisable compounds may be ignored. Titration may be made with deci-normal or with hundredth normal thiosulphate or with even weaker solutions, allowing determination of as little as 0.1—0.5 mgms. of alcohol.

SUMMARY.

1. Provided that the temperature, arterial resistance and venous inflow be maintained constant, the action of drugs on the functional capacity of the heart muscle is revealed in the heart-lung preparation by a change in the systolic and diastolic volumes of the ventricles, an improvement being shown by diminution, an impairment by an increase in these volumes. The worse the physiological condition of the heart, the greater must be its initial or diastolic volume in order to carry out a given task, viz., the expulsion of a given amount of blood against a given resistance.

2. Judged by this criterion there is no evidence of any stimulant effect of alcohol on the heart in any doses. With concentrations of alcohol in the blood as low as 0.06%, the only effect observed is an increase in diastolic and systolic volumes, and this effect becomes more and more marked as the concentration of alcohol in the blood is increased. The action of alcohol on the heart muscle, as soon as any effect whatever is produced, is thus purely depressant.

3. With higher amounts of alcohol, such as 0.3 or 0.4%, there is a diminution in the output of the heart, and a considerable rise in venous as well as pulmonary pressure.

4. In concentrations of 0.1 to 0.2% onwards, alcohol causes the coronary vessels to constrict and to reduce the coronary flow.

5. A method is described for the rapid and accurate determination of alcohol in small quantities of blood.

I wish to express my indebtedness to Professor Starling for his help and advice throughout this investigation.

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STUDIES OF CAPILLARY PULSATION, WITH SPECIAL REFERENCE TO VASODILATATION IN AORTIC REGURGITATION AND INCLUDING OBSERVATIONS ON THE EFFECTS OF HEATING THE HUMAN SKIN.*

By THOMAS LEWIS.†

(With appended notes on skin temperature, in collaboration with
Dr. E. P. WOLF, of Chicago.)

(From the Cardiac Department, University College Hospital Medical School,
London.)

PRELIMINARY REMARKS UPON THE EFFECTS OF HEAT ON
THE HUMAN SKIN.

If the hand of a young subject is soaked in hot water for 3 minutes at a temperature of between 45 to 47°C. the part immersed becomes of a bright red colour, and this reddening is maintained for from a few minutes to even an hour or more after withdrawing the heat. The temperature used is that which begins to produce stinging of the skin, a point which does not vary greatly from subject to subject. In the human skin this colour reaction to heat can be shown to be at least of two-fold origin.

First method. The circulation to the arm is occluded by placing a broad armlet on the upper arm and pumping it to 200 mm. Hg., previously allowing a little blood to collect in the veins. The lower part of the forearm and hand is now soaked in hot water at 43°C. for 3 minutes. It is necessary to use a temperature slightly below that which stings the arm when the circulation is intact: otherwise the heat becomes intolerable as the soaking proceeds, presumably because the skin is not cooled internally by circulating blood. The arm should be held absolutely still in the water. At the end of 3 minutes, and before releasing the circulation, the skin is seen to be cyanosed and the soaked area to be of a darker colour than the unsoaked area, there being often a fairly sharp line of demarcation between heated and unheated surfaces. This observation shows that the heat dilates those small vessels, such as capillaries and minute venules, which are responsible for skin colour.

* The matter of this paper was collected for, and discussed in, the Sidney Ringer Lecture at University College Hospital Medical School, on March 6th, 1924.

† Working on behalf of the Medical Research Council.

Second method. An armlet is placed on the upper arm and pumped to 70 mm. Hg., and the forearm is half immersed and held quite still in water at about 45°C., for 3 minutes. On examining it at the end of this time, the unheated skin is seen to be cyanotic, while the heated skin is of a bright red colour, departing little from that of heated skin in which venous pressure has not been raised. The line between heated and unheated areas is sharply defined by the colour reaction. To account for the absence of cyanosis in the heated skin it is necessary to assume that the blood flows through it quicker. Simple dilatation of the capillaries and minute venules, such as is produced by suction, flushes the skin, but this flush soon acquires a blue tinge, the more so if venous pressure has been raised simultaneously, for in these circumstances the blood passes slowly through the skin. The bright colour of the heated skin in our present experiment can be accounted for only if, in addition to raised venous pressure, there is a dilatation on the arterial side. This dilatation is evidently arteriole in so far as responsibility for redness of the skin is concerned, since the red skin is sharply marked off from the blue at the water line and because it can be produced by very local heating. When the forearm and hand are heated, dilatation of some at least of the main arteries of the limb occurs: thus, the volume of the digital pulse is increased; conceivably this dilatation of main arteries also plays a small part in reddening the hand. Visible expansion of a larger artery, in response to heat applied, is best displayed by the superficial temporal vessel.

The reddening of the hand exposed to temperatures of 45-47°C. is a direct action and independent of the nerves. If a patch of skin an inch in diameter is rendered anaesthetic by the subcutaneous injection of 2% novocaine, and the whole arm is then immersed and held in water as hot as can be borne without actual discomfort (45-47°C.) for three minutes, at the end of this time the anaesthetic skin cannot be recognised by its colour. (Observations on three subjects).*

Thus reddening of the human skin on exposing it to moist heat at 45-47°C. is a local reaction, and due, mainly at all events, to arteriolar dilatation: the depth of skin colour is increased by simultaneous and independent dilatation of the capillaries and small venules.†

Effect of higher temperatures. Continued immersion at temperatures appreciably higher than those cited is not possible, since such immersion is intolerably painful. To test the effects of higher temperatures, a test tube is filled with boiling water and is brought into contact with the

* It is to be stated that the local injection itself often reddens the skin a little, thus complicating the result. I have since repeated the observation upon a case of long standing division of the ulnar nerve. On heating the hand, the insensitive skin was not recognisable from the sensitive, both being of the same bright red colour.

† Bruns and König† have examined the human skin, reddened by a temperature of 42°C., and have noted increased flow in the capillaries, widening of the subcutaneous veins and pulsation of the digital arteries. Carrier has shown that heat dilates the capillaries and increases the rate of flow through them.

skin a number of times for short periods. The reaction to this stimulus is best displayed by previously congesting the arm at 70 mm. Hg. until it becomes cyanosed: the skin reaction to heat is then seen as a bright red patch on a bluish surface, indicating arteriolar dilatation. Heat so applied produces pain, and is followed by a spreading reaction, the skin eventually reddened being many times in area that of the skin actually heated, having an irregular outline, and affecting often outlying islets of skin. The distribution of this reaction at once suggests its reflex origin, and this is easily shown if the test is repeated on skin locally anæsthetised by subcutaneous novocaine. A small area is anæsthetised and this is reddened where the hot tube has touched it; spread to distant parts of the skin does not occur. (Observations on two subjects.*)

CAPILLARY PULSATION AS A NORMAL PHENOMENON.†

Amongst phenomena originally described by clinicians as physical signs of disease, and consequently regarded as essentially morbid, very many have afterwards been recognised to occur in perfectly healthy people; it would not be difficult to draw up an imposing list in illustration of this statement. It must be said that for the most part such phenomena appear in a more or less limited number of healthy people or in special physiological circumstances. Thus the "extensor response" in infants, and "respiratory arrhythmia" in children, is normal. The "tâche cerebral" is the normal reaction of young and sensitive skins to stroking, so also is whealing of the skin in response to heavier or repeated stroking. Systolic murmurs are normal and almost usual over hearts accelerated by exercise; the "pulsus paradoxus," as originally defined, is the usual and physiological reaction of blood pressure to breathing in the resting subject. The erroneous categorisation of such natural phenomena is brought about by a faulty habit of mind which is content to associate symptoms and signs with particular diseases, without attempting further to analyse causation; it is a postponed and more intimate study, a belated comparison of the disease with controls, the last in sufficient numbers and under varying physiological conditions, which brings us more correctly to interpret the manifestations in question.

It may not be precisely true to state that capillary pulsation is to-day generally regarded as a positive indication of reflux at the aortic valves; it is certainly true to state that this correlation between a phenomenon of skin or mucous membrane on the one hand and a defective valve on the

* Krogh¹⁴ briefly refers to some unpublished observations with Reiberg on the rabbit's ear and states that they have found that heat produces dilatation, in part by a local mechanism and in part reflexly. The temperature mentioned is 50°C.. Ricker and Regendanz* had previously shown that dipping the upper third of a rabbit's ear in water at 52°C. produces widening of the arteries and œdema, and that the vessels in the base of the ear are also widened. Effects of burning heat on the skin will be more fully described in a future paper.

† A preliminary account of these observations has been published in the *Proc. Physiol. Soc.*, December 15th, 1923.

other, is the only clear impression in regard to the sign which is possessed by the vast majority of medical men. Yet, as may be shown, capillary pulsation as we witness it clinically is wholly unreliable as a sign of aortic regurgitation and depends more upon strictly local conditions than upon any change of general arterial blood pressures arising out of a damaged valve.

Some years ago I examined the lips of 35 subjects, ranging in age from 20 to 40 years and free from cardiovascular disease, and found capillary pulsation to be perceptible in 17 of these. These observations were made during the colder months of the year, a fact not without relevance. Had all these subjects been warm when examined, and many were not, the percentage incidence would have been greater. In this series the phenomenon was quite unrelated to pulse pressure, gauged in the arm in all instances. Usually the pulsation was slight and required carefully graded pressure with a glass slide to elicit it: in a few it was very distinct and could be seen at almost any pressure. Recently I have examined five normal men lying quietly in a room whose temperature was 20°C.; distinct pulsation in the lip was present in all, and in all it could be seen also in several parts of the facial skin. In six similar subjects lying in a room at 17°C. there was also no exception either so far as lips or facial skin was concerned. I have seen capillary pulsation so often in the face of out-patients that the list, expressed in terms of disease, has become entirely meaningless.

In the hands the pulsation is less frequent, though by no means rare, the parts displaying it are usually the pads of the fingers, or these and other parts of the skin, such as that behind the bed of the nail or over the thenar and hypothenar eminences. Frequently I have found it in my own fingers and in those of my friends, especially so while sitting near a fire. In this connection it will be remembered that Quincke¹⁷ noticed centripetal pulsation in the veins on the back of his own hands in similar circumstances. Capillary pulsation, whether it be in the lips or hands of normal people, is much more frequently found in children and young adults than in those more advanced in years: its obvious connection with warmth of the hand led me to search the influence of temperature systematically. The hand is first examined before heating it, a glass plate being pressed against the pads of the fingers, over the eminences of the palm, over the skin behind the nail bed, over the knuckles, and dorsal surface of the metacarpus. It is then laid in water as hot as may be borne for three minutes. This temperature, enough to sting the hand, lies almost always between 45 and 47°C.. The hand is dried and at once re-examined. Capillary pulsation is then generally to be seen in it. If it is found only on close inspection, and then usually confined to the pads of the fingers, the phenomenon is marked "slight" in Table I. If it is quite distinct in the finger tips and slight in a few other parts of the hand, such as the thenar or hypothenar eminences, it is marked + in the table. If it is distinct or vivid in the finger tips, and if it occurs also distinctly over the whole, or over many parts, of the heated skin on the palms and dorsal surface

TABLE I.

Reaction of hand to hot water at 45 to 47° C. for 3 minutes.

No.	Age.	Capillary pulsation.	Blood pressure.		Pulse pressure.
			syst.	diast.	
1	17	.	135	95	40*
2	19	++	110	75	35*
3	23	++	126	86	40
4	24	++	130	85	45*
5	25	++	115	80	35
6	25	++	138	95	43
7	27	++	125	90	35*
8	29	++	130	100	30
9	30	.	118	90	28
10	31	++	135	85	50
11	32	.	115	85	30
12	34	++	104	70	34
13	35	.	138	90	48*
14	35	.	115	85	30
15	38	++	118	85	33*
16	38	sl.	115	85	30
17	39	.	135	85	50
18	41	+	118	85	33
19	42	+	127	88	39
20	43	.	124	85	39
21	43	sl.	158	115	43
22	46	+	132	87	45
23	46	sl.	135	90	45
24	46	sl.	124	95	29
25	46	0	125	95	30
26	52	+	145	100	45
27	53	sl.	125	85	40†
28	56	sl.	136	87	49†
29	57	.	125	75	50†
30	57	0	125	90	35
31	57	+	145	95	50
32	60	+	145	90	55†
33	60	+	140	90	50
34	60	++	138	95	43*
35	61	0	140	100	40
36	61	0	120	95	25
37	74	0	105	55	50†
38	76	0	148	92	56†
39	84	sl.	124	95	29

of hand and fingers it is marked ++ in the table. In the last columns of the table, the blood pressures are given and, with one possible exception, these are normal. Between the appearance of capillary pulsation in the heated hand and the pulse pressure no relation is here shown: but there is an obvious though not wholly constant relation to age. Those who range from 17 to 35 years display capillary pulsation most fully and with much uniformity in its degree. As age advances into and beyond the forties it becomes less evident than in young people and many instances are found

* Pulsation present in one or more finger tips before heating.

† Patients, mainly surgical, admitted for maladies unconnected with the cardiovascular system.

in which it is but slight and confined to the finger tips, or in which it is altogether absent. A single exception to the rule that distinct and widespread pulsation fails to appear after 45 years was observed in an active man aged 60. The occurrence of capillary pulsation in the hand when it is heated is evidently consequent upon a local change: and is inevitably attributed to dilatation of the blood vessels. The constancy of the reaction in young people, and its inconstancy in the more elderly, indicates that in the latter dilatation, or at least sufficient dilatation of the particular vessels involved to produce capillary pulsation, does not occur on heating, and further suggests that those vessels are incapable of expansion, relatively or absolutely. The idea is put forward that the appearance or non-appearance of capillary pulsation in the circumstances described, may serve to test the condition of the vessels in question. Although most of my observations have been upon the skin of the hand, they have not been confined to it; in young people capillary pulsation if not already present may be elicited with ease in the lips and in the skin of the forehead, cheeks, foot, and in other parts, by sufficient bathing with hot water.

As to the vessels involved, the matter is easy to test in the case of the hand. Dilatation of the main arteries of the limbs plays little or no part. Thus, if the whole arm be laid in a hot bath, with the hand or the fingers projecting above the water level, capillary pulsation is not induced in the unimmersed fingers, although the volume of the radial and ulnar pulses may be noted to be increased. If the arm and hand are immersed with the exception of the last joints of several fingers, so that the main arteries of the hand and fingers are likewise influenced by the heat, pulsation is not produced in these finger tips: the last test is sometimes complicated, however, by the appearance of coldness and pallor of the finger tips, a reaction which may be of a reflex kind but is more probably due to a mechanical diversion of the blood from them. If the wrist is flexed and the hand immersed alone with the dorsum downwards, so that the finger tips are again unheated, or if a finger is flexed and alone immersed with its tip projecting, coldness or pallor of the end of the digit is not noticed subsequently, and pulsation is confined to the submerged parts of the skin; nevertheless in these tests the digital arteries are perceptibly widened. If the last phalanx of a finger, or no more than the pad of a finger, is dipped in the water, pulsation appears in the part heated. The area which it is necessary to heat is very small; thus when a beam of unfiltered light, sufficient just to sting, is allowed to fall on the skin above the bed of the nail for a few minutes, being confined to 10 or more square millimetres of the surface, the skin throbs perceptibly to the subject and capillary pulsation appears in this small area. It is clear, therefore, that the vessels involved are amongst the smallest which supply the skin. That those capillaries and minute vessels, which together yield skin colour, do not primarily determine pulsation is shown by the absence of the last from skin which is pink or red in response to cold, and from the skin of middle-aged or elderly subjects in whom capillary

pulsation fails to appear on heating; for in the latter the skin may be well reddened by the heat. It is evident that the vessels determining the reaction are the arterioles of the skin.

These observations show how capillary pulsation may be induced in very small areas of the skin artificially; comparable instances are found in pathological conditions presently to be instanced. It may be stated as a general law that when normal blood pressures prevail in the main vessels supplying an area of skin, a sufficient dilatation of the smaller vessels on the arterial side will always occasion capillary pulsation in the presence of open capillaries and venules. This generalisation is justified by the observations detailed already and by those which come later. The qualification "open capillaries and venules" is necessary. Unless the skin has some flush of colour in it, capillary pulsation will not be seen. The contrary statement, that a flushed skin will necessarily exhibit capillary pulsation, naturally does not hold. A flushed skin is brought about in one of several ways. If the arterioles are open and the tone of capillaries and venules is normal, the flush has an arterial colour and is hot; it is in such that capillary pulsation is best seen. If the arterioles are narrow, but capillaries and venules lack tone, the blood flow through the last two is slow and the flush has a more or less blue tinge. In skin which has a bluish flush capillary pulsation is not found. Thus, a hand which has been soaked in cold water ($12-15^{\circ}\text{C}.$) is often redder but colder than the unsoaked hand soon after withdrawing it from the water; in these circumstances the warm hand only can exhibit pulsation. An illustration of this fact is given later in this paper.

The examples which have so far been cited are all conditions in which vasodilatation, general or local, is not to be denied; the idea that widening of the arterial channels leads to a pulsatile flow of blood in the smaller vessels of the tissue supplied is not new: it dates back to the time of Claude Bernard¹, and has been discussed by other writers since^{9 & 11}.

Further, to illustrate the relation between capillary pulsation and dilated arterioles, small inflammatory lesions of the skin may be instanced. In young healthy men, capillary pulsation may be found confined to the immediate neighbourhood of small cuts or scratches, such as have been produced in shaving; especially is this the case if such cuts or scratches are in an inflammatory stage and stand surrounded by small areas of hyperæmic skin. I have examined several cases of slight and fresh herpes labialis in young people, otherwise normal, and in these have found no difficulty in detecting pulsation. Glaessner⁹ has seen capillary pulsation in small acne pustules; I have also seen it in all of the several cases I have examined. In instances of this kind the phenomenon is strictly local, and can be ascribed only to dilated skin vessels of small calibre. These local lesions when tested are shown to have a higher temperature than has the surrounding skin (see Appended note F). There is a relation between perceptible throbbing of such lesions and the appearance of capillary pulsation in them.

A healthy lad of 19 years was examined shortly after returning from a brisk walk on a cold day; his face a little flushed by exercise. Slight capillary pulsation was found in the lip, skin of forehead and cheek. A capsule of amyl nitrite was administered and, at the height of a good reaction, vivid pulsation was seen in the same areas; ten minutes later pulsation was slight in the lips, but was found nowhere else; the skin colour was now normal. A young and healthy medical student inhaled a capsule of amyl nitrite; the flush soon appeared over his face, but was not intense; at the height of the reaction capillary pulsation was distinct in the forehead and cheek and more intense in the lip. This student told me that he had observed capillary pulsation in his skin, in small erythematous areas caused by the bites of insects. A capsule inhaled by a healthy man of 39 years produced capillary pulsation of the lip, but none could be detected over the forehead or cheek.

Recently a young woman of 28 years consulted me for attacks of palpitation and daily feelings of exhaustion in her work as a typist; these symptoms were associated with poor appetite and sleeplessness. Apart from a little quickness of the pulse and an occasional extrasystole, the heart seemed normal. She was examined in a cold room. Over the whole of her face, neck and the upper part of the chest a vivid and scarlet flush was seen, persistent during the examination. This skin was hot to feel, and the patient stated that her face burned and throbbed; in subsequent tests (Appended note D) it was ascertained that the facial skin temperature was well above normal. Over the whole face, in the lobes of the ears and in the lips, a very distinct capillary pulsation could be seen; it was present in lesser degree in the reddened skin of the neck and chest. The brachial blood pressure was 128 systolic and 90 diastolic. On stroking her back with a blunt point, a vivid and spreading *tâche* developed, and this also exhibited obvious pulsation. I have since seen vivid pulsation in small areas of bright erythema developing spontaneously, in one case on the cheek and in the other on the neck, of two young women.

A familiar method of displaying the capillary pulse in aortic disease is to rub the skin or to stroke it firmly with a blunt point; this procedure increases the temperature of the skin, dilating the arterioles (see Table IV). In patients who display "urticaria factitia," stroking of this kind yields a central red line around which a bright and irregular erythema soon appears; the central line eventually becomes oedematous. The erythema, as has been shown, is due to reflex dilatation of the arterioles; it involves not only the surrounding skin but the central line of oedematous tissue. In six examples of the kind, examined for the purpose, a distinct or vivid capillary pulse was found in each instance. It was present in the surrounding flush and in the wheal itself. In three of these the rise of skin temperature was tested; it rose on the line stroked by from 1.5 to 2.5°C., respectively (see appended note G).

Quinke¹⁷ and others have recorded many instances of capillary pulsation in the skin of febrile patients. Glaessner⁹ found it in the flushed skin of Grave's disease, and attributed it in large part to vasodilatation; it is now well recognised to occur commonly in that disease.

CAPILLARY PULSATION IN AORTIC REGURGITATION.

Areas in which capillary pulsation appears.

The capillary pulsation of aortic disease may appear in any part of the skin of the body under suitable conditions. Thus, it can be induced almost anywhere by friction or the application of heat. Looking at the skin in cases of free* aortic regurgitation as these come to an out-patient department, there are a few areas where capillary pulsation is usually distinctly visible without touching the skin: these are the forehead and cheeks. In some cases, not so uncommon as they are usually believed to be, the reddening of the face with each systole and its paling with each diastole are so distinct that they may be visible at a considerable distance from the patient. More usually the pulsation is detected only after closer inspection, the light being allowed to fall at different angles on the face. Such *spontaneous* capillary pulsation is more frequent in patients who are standing than in those who are lying in bed: it is rarely seen in skin other than the facial. The finger tips and palms of the hands show a similar pulsation from time to time, especially when they are held aloft,† and I have seen a few instances in which the spontaneous flush was visible over the whole hand, back and front. It is customary to search for capillary pulsation with the aid of a glass slide, the skin or mucous membrane of the lip being pressed until it pales a little. This procedure often discovers pulsation in a surface which otherwise maintains continuously a full colour. If the superficial vessels are well distended, pulsation in them does not greatly alter their volume unless such outside pressure is exerted as to reduce them in size materially during the diastolic phase: they then swell in systole. When a glass slide is used, capillary pulsation is often found in the hand, though by no means so frequently as in the face. In the hand the pads of the fingers and thumb show it most frequently, and after these the thenar and hypothenar eminences, the skin above the nail bed, and the remaining palmar surfaces of hand and finger in approximately this order. Beneath the nail itself it is not so common or so vivid as in other parts, hardly more common, in fact, than upon the dorsum of the hand. Clinicians use the nail as a rule: they do so because the nail substitutes the glass slide: it is not a very favourable place in which to display pulsation.

Broadly speaking, capillary pulsation occurs only in those parts of the unstimulated skin which are ordinarily exposed to the atmosphere and are

* By which I mean cases in which there is high pulse pressure and well-developed water-hammer pulse.

† A change of position which is reputed to dilate the arteries.

particularly vascular, namely, in the skin of the face and hands. The main exception to this rule is the foot. Here pulsation, though far less frequent than in the hand and still less frequent than in the face, is not very uncommon. It occurs in the pads of the toes and over the lower surface of the heel most often and, after these, in the remaining portions of the foot which are exposed to pressure, the sole and small portions of the borders of the foot. The skin over these parts of the foot is ridged and especially vascular.

Relation between capillary pulsation and pulse pressure.

In studying cases of arterio-venous anastomosis in conjunction with Drury¹⁶, capillary pulsation was found in the skin and in the lips. This was not surprising since all the remaining signs customarily met with in the arterial system in cases of aortic regurgitation, including low diastolic and high pulse pressure, were present. We were surprised to find, however, that, on cutting the A-V anastomosis out of the circulation by compressing the artery running to it, and thus restoring the pulse pressure to normal limits, the capillary pulse persisted in apparently its original degree. We were forced to conclude that capillary pulsation is not determined by high pulse pressure in cases of arterio-venous anastomosis.

If a group of aortic cases is examined in the ordinary clinical way, it quickly becomes evident that a relation between the magnitude of the pulse pressure in the brachial artery and the degree of capillary pulsation in the hand cannot be demonstrated satisfactorily. Different cases with similar pulse pressures display either vivid pulsation, no pulsation, or any intermediate state. Many cases with relatively high pulse pressure present no capillary pulsation, others with relatively low pulse pressures may display it distinctly. Such observations at once suggest that there are factors controlling the intensity of capillary pulsation in aortic cases which weigh as heavily or more heavily than does pulse pressure. The matter may be put to a direct test in aortic regurgitation, as in arterio-venous anastomosis, by altering the available pulse pressures in individual cases. In aortic disease the following method may be used. Cases are chosen in which capillary pulsation is easily to be seen in the hand and this pulsation is watched while the corresponding brachial artery is partially obstructed.

Thus, in a case of syphilitic aortic disease, in a man of 49 years, the pressures in the brachial artery were 210 (systolic) and 70 diastolic. On pressing the palm of the hand with a glass slide, capillary pulsation was at once manifest and vivid. With the arm semi-dependent the armlet pressure was now raised abruptly to 180 mm. pressure. The pulse beats forced their way through the armlet at this pressure, though naturally they were much diminished in volume; they were transmitted to the small vessels in the palm of the hand, capillary pulsation being distinct in it. When in a fresh observation the armlet pressure was raised to 190, capillary pulsation could not be discerned. The method has the disadvantage of often showing

capillary pulsation for a short while only, the pulsation disappearing as the venous pressure rises to its height; it also has the disadvantage that the actual strength of the beat reaching the hand cannot be estimated as a pulse pressure in millimetres of mercury. Therefore it was varied. The armlet was eventually raised to 170 mm. Hg.* and thus maintained for 3 minutes, allowing the veins to become fully engorged to that pressure. Capillary pulsation though much lessened in the hand remained just distinct. The water-hammer quality of the pulse was naturally lost. The available pulse pressure in this observation could not have been far removed from 40 mm. Hg.. When repeated with an armlet pressure of 180, capillary pulsation was not seen.

In a young man, suffering from free aortic regurgitation, and having brachial blood pressures of 135 (systolic) and 35 (diastolic), the armlet was maintained at 90 mm. for $2\frac{1}{2}$ minutes; the veins then stood out as hard cords; capillary pulsation, previously very distinct in the hand, decreased but was just perceptible. The armlet pressure was now dropped to 80 mm.; the veins lost a little of their tension and the pulsation now became perfectly plain. Under both conditions the water-hammer character of the radial pulse was lost, the pulse being small; the available pulse pressures in the two observations were 45 and 55 mm., respectively.

In a third patient, a man of 27, the subject of subacute infective endocarditis of the aortic valves and showing unusually vivid capillary pulsation in the palms of the hands and fingers, the brachial pressures were 132 (systolic) and 55 (diastolic). Compression of the upper arm at 90 mm. for 3 minutes and for an additional minute at 100 mm., left the intensity of the capillary pulsation seemingly almost unchanged. The water-hammer quality of the pulse was lost and the pulse became small, the available pulse pressure being only 32 mm. Hg..

These examples, repeated with like results on several other patients, are sufficiently illustrative of the method and its results.

The following observation affords evidence from a similar point of view. W. K., a man of 48 years, suffered from syphilitic aortitis, from which he ultimately died. The heart was enlarged and the aorta dilated; there were signs of free regurgitation through the aortic valves. The pulse in the arteries of the left arm was water-hammer in character, the average of numerous blood pressure readings being 149 (systolic) and 35 (diastolic). The pulse in the right arm was small and anacrotic in type, palpably and in optical records; the average blood pressure readings in this arm were 104 (systolic) and 48 (diastolic). Thus the pulse pressure was 114 in the left arm and 56 in the right arm. The blood flow to the two forearms, measured by Hewlett and Zwaluwenberg's method was equal, namely, 43 cc. per minute. The carotid pulses were also unequal, being notably smaller on the right side than on the left. An obstruction in the innominate artery was naturally diagnosed and

* To obtain a quick and complete engorgement of the veins, it is best to allow them first to fill at a lower pressure.

ascribed to the syphilitic disease of the aorta. Spontaneous capillary pulsation was present in both cheeks and across the whole forehead; in the left cheek, however, it was more vivid than in the right. The lip, pressed with a glass slide, presented uniform and conspicuous pulsation. A firm stroke on the skin of each forearm was followed by a red line in which capillary pulsation was to be seen; the pulsation was again more vivid on the left side. The interest in this aortic case is the presence of capillary pulsation in head and arm on the right side, despite the normal pulse pressures prevailing there, and in this respect the case is an important confirmation of the previously cited observations, since it avoids the complicating factor of venous congestion. The greater degree of capillary pulse on the left side may be explained in one of two ways: either the higher pulse pressure on this side contributed, or the factor responsible for capillary pulsation on the right side, a factor other than high pulse pressure, was acting more intensely on the left side. This question remained undecided.

These examples show unmistakably that an increased pulse pressure is no more essential to the production of capillary pulsation in cases of aortic regurgitation than it is in cases of arterio-venous anastomosis and that another factor must be found before the capillary pulsation of aortic disease receives adequate explanation. It may be true, however, even if the chief determining factor is not high pulse pressure, that the last contributes.

In attempting to discover whether the degree of capillary pulsation is related to the magnitude of pulse pressure, it is clearly necessary, as in all similar comparisons, to render other factors which come into play constant. It has been seen that capillary pulsation may be readily induced in normal subjects by any means which dilates the arterioles. Before we can thoroughly examine the interrelation of capillary pulsation and pulse pressure in aortic disease, the arteriole factor must be rendered constant. Probably we come nearest to doing so when we produce in young subjects, exhibiting various pulse pressures, a full vascular dilatation by such an agency as heat. Thus, if we use such a series, and immersing the hand in water at temperatures sufficient to sting the skin (45-47 °C.), measuring the blood pressures in the arm while the hand is hot and examining the capillary pulsation shown, we obtain results such as those shown in Table II. In a series of normal men of similar age period, we anticipate finding distinct or vivid capillary pulsation in the finger tips and distinct pulsation over the whole, or over many parts, of the heated skin on the palmar and dorsal surfaces of the hand and fingers; we anticipate, therefore, to find at least these grades in our young cases of aortic disease. In the present table the first five patients presented at least this degree of pulsation; actually the pulsation in this group as a whole was somewhat more extensive than is seen in normal subjects, being distinct over the whole heated skin in each instance. The pulse pressures in these patients ranged from 49 (a normal value) to 80 mm. Hg.. In the next two cases the pulse pressure was 90 and 92 mm. Hg., and in these distinct or vivid pulsation was found in all parts of the heated

TABLE II.

*Various grades of aortic regurgitation in young men.**Hand in hot water at 45-47° C. for 3 minutes.*

No.	Age.	Brachial blood pressure.			Capillary pulsation in hand.
		syst.	diast.	pulse.	
1	25	132	83	49	Distinct everywhere.*
2	31	152	85	67	Distinct everywhere.*
3	31	155	80	75	Distinct everywhere.*
4	27	145	70	75	Distinct everywhere.*
5	31	145	65	80	Distinct everywhere.*
6	31	165	75	90	Vivid or distinct everywhere.
7	28	152	60	92	Vivid or distinct everywhere.
8	33	165	55	110	Vivid everywhere.
9	28	160	40	120	Extremely vivid everywhere.
10	29	180	45	135	Distinct everywhere.*

* The pulsation was equal in degree, but more extensive than that found in the normal subject under similar conditions.

TABLE III.

*Free aortic regurgitation in older men.**Hand in hot water at 45-47° C. for 3 minutes.*

No.	Age.	Brachial blood pressure.			Capillary pulsation in hand.
		syst.	diast.	pulse.	
1	44	182	75	107	Vivid everywhere.
2	68	158	50	108	Vivid everywhere.
3	60	192	90	102	Vivid or distinct everywhere.
4	46	190	68	122	Vivid or distinct everywhere.
5	54	158	48	110	Distinct everywhere.
6	41	160	45	115	Distinct in finger pads and palm and nail bed only.
7	45	166	65	101	Distinct in finger pads and palms only.
8	68	165	60	105	Absent.

skin ; the degree of pulsation was decidedly greater and it was more extensive than is seen in normals of the same ages. In the next two cases the pulse pressures were 110 and 120 mm. Hg. respectively, in the first instance vivid pulsation was everywhere visible, in the last the pulsation was exceptionally vivid in all parts and occurred spontaneously over the whole hand. It is clearly true that when the heated hands of normal men and of aortic cases are compared, capillary pulsation is in the rule more intense in the aortic series. It is also the rule that the pulsation becomes more intense and widespread as the pulse pressure increases ; a single and notable exception to this statement is found, however, in the last case of the table. In a man, whose pulse pressure was 135 mm. Hg. the capillary pulsation in the hand was no more intense, though somewhat more extensive, than in a normal subject of the same age. Such discrepancies between the pulse pressure and the degree of capillary pulsation are more common in patients of more advanced years, as Table III shows. These patients were chosen for their age and because in all the pulse pressure exceeded 100 mm. Hg.. Evidently, in such there is a variant similar to that found in elderly but normal subjects (Table I), namely, an arteriolar factor. Variation in the number and distensibility of the arterioles is not within our control. If we assume that only two factors come into play in producing capillary pulsation, namely, pulse pressure on the one hand and the state of the arterioles on the other, and if we further assume that arterioles are brought to a sufficiently constant state of dilatation by heating the skin in all healthy young subjects, and in almost all young aortic cases, while it fails to do so in a goodly percentage of older subjects, then we seem to possess an adequate explanation of capillary pulsation as this is displayed by the heated skin.

To sum up : a heightened pulse pressure in aortic regurgitation is not an essential cause of capillary pulsation : given, however, that the remaining conditions are suitable to induce capillary pulsation, then this pulsation varies in its degree with the pressure amplitude of the pulse wave. The suggestion that the state of the arterioles plays a chief part in producing capillary pulsation in the unheated skin may now be examined further.

The arteriolar factor.

Relation of capillary pulsation to skin temperature. The presence or absence of capillary pulsation in a particular area of skin is closely related to the temperature of that skin. In observations upon a large number of patients presenting evidence of free aortic regurgitation, I have noted no exception to the rule that, other conditions being equal, capillary pulsation is best displayed by areas of skin which feel warm or hot. In such observations those comparisons are most valuable where symmetrical areas of skin, being equally supplied by vessels, are found to have different temperatures. In a general and somewhat less accurate way we may compare skin areas of the face with each other or with those of the hand. Spontaneous

capillary pulsation does not occur in the skin of the face unless the area showing it feels warm or hot ; the warmest part of the face will show capillary pulsation to best advantage and this is usually the cheek or forehead. The lobes of the ears are often cool or cold ; in such, little or no pulsation can be elicited until they are warmed and brightened in colour by rubbing or by exposure to a warm room temperature. Sometimes the nose or chin is cold or cool while the rest of the face is warm ; then capillary pulsation is found in the last only, or will be far less vivid in the first. Not infrequently at an examination one cheek may be found hot and the other cold : in the former capillary pulsation is found, in the last not. If the hands are cold, capillary pulsation is not to be seen in them ; if they are warm, it is there. I could cite a score of cases, examined clinically, in which these broad rules hold true. In many cases, by feeling the skin in several regions and comparing the temperatures so gauged, the relative degrees of capillary pulsation which will be found can be predicted approximately. To display the relation between skin temperature and capillary pulsation in cases of free aortic regurgitation more precisely and more objectively, a thermo-electric couple has recently been employed. This amply confirms the clinical observations ; showing as it does how closely, in cases treated individually, varying skin temperatures and corresponding degrees of pulsation are associated (see Appended note B). It is clear from these observations that unless the presence or absence of capillary pulsation is correlated with the temperature of skin or mucous membrane in which it appears, it can have little or no value as a sign.*

I have already indicated that external temperature influences the appearance of capillary pulsation. It does so by widening or narrowing the arterioles of the skin. This relation to external temperature is easy to display in cases of free aortic regurgitation. Soak the hand of a young patient for 3 minutes in baths of water at suitable temperatures and almost any grade of capillary pulsation can be produced. The following broad experiment, twice repeated on the same subject with very similar results, will serve as an illustration.

In a man of 29 years, lying in bed in a ward whose temperature was 21°C ., the brachial blood pressure was 180 (systolic) and 40 (diastolic) : the hand felt just warm and the finger tips and palm showed distinct capillary pulsation on pressure. The arm was placed in a bath of water at 36.8°C . for 3 minutes ; the blood pressures were now 172/45 and capillary pulsation was unaltered. It was now soaked in water at 45°C . for 3 minutes, after which the whole hand (back and front) flushed spontaneously with each systole. It was now placed in water at 26°C . for the same period : the blood pressures became 165/40 and slight pulsation was visible in the hypothenar eminence, but in no other part of the hand. By varying the temperature of the water, the extent and degree of the pulsation could be varied at will. From day to

* A statement which, incidentally, applies with almost equal force to cyanosis as a sign.

day, however, the lower temperatures would not always bring the hand into precisely the same states, though the blood pressures were remarkably stable. The tone of the skin vessels was not entirely determined by external temperature. In the same patient, and in many others, it has been easy to show that it suffices to warm or cool surfaces of quite small extent locally to modify the degree of capillary pulsation. If a hand is heated to 45°C. while a single finger tip is cooled (10-20 °C.), the cooled finger tip will show no pulsation, while its neighbours will show it vividly. Similar observations have been carried out, with like results, upon the skin of the face, the foot, etc.. In aortic cases capillary pulsation is particularly conspicuous where the skin is reddened by small lesions such as small cuts on the chin, herpes of the lip or in small acne papules: often it is found vividly in these when there is no visible pulsation in the surrounding skin. As in normal subjects, the temperature of these little inflamed areas is higher than that of the surrounding skin (see Appended note F).

Temperature affects capillary pulsation in aortic disease as it does in normal subjects. The comparison in its detail serves to demonstrate that a factor governing the degree of capillary pulsation, as we see it in aortic disease, is the condition of the arterioles. It has been shown that external temperature profoundly modifies the events: whether we succeed or fail to find capillary pulsation in the hand, for example, will largely depend on the temperature of the room in which a patient is examined: capillary pulsation is more often seen in summer than in winter.

Now the relation between skin temperature and the condition of the arterioles is open to two interpretations. On the one hand, a change of external temperature, by changing that of the skin, will alter the size of the skin arterioles, and our last illustrations evidently belong to this category: on the other hand, a warm or cold skin may be due primarily to the state and distribution of the arterioles. That must be the case where, for example, various areas of the facial skin present different temperatures, though exposed to the same room temperature. Here the relative degrees in which pulsation is exhibited is determined primarily by the state of the arterioles.* Obviously it may be concluded that in any given case of aortic regurgitation those areas which present capillary pulsation are areas in which the arterioles are dilated as compared to those of areas which show none. A more interesting question, and one which necessarily arises, is whether the arterioles in areas showing pulsation in this valvular defect are more dilated than are the arteries of corresponding areas in normal subjects. In other words, are there areas of active arteriolar dilatation in aortic disease? Some evidence to this effect has been produced already: for it has been shown that in cases of very distinct capillary pulsation of the fingers, the pulsation may be independent of pulse pressure, and is then due presumably to abnormal widening of the arterioles. Further evidence may now be examined.

* Not wholly, however, see Appended note B.

Skin colour and temperature in aortic disease.

Other things being equal, the colour and temperature of the skin are controlled by the state of the arterioles, widening of which flushes the skin. While a bright red colour of the skin is usually a sign of arteriolar dilatation, an unflushed skin does not negative widened arterioles. It has been pointed out by Ebbecke⁷ that the skin may be warm and at the same time pale. Dale and Richards⁶ noted in the cat that a paler paw might give off more heat than a redder paw. The blood lying in the superficial plexuses is mainly responsible for skin colour, so that an arteriolar dilatation will yield the characteristic flush only if the capillary and venule tone is normal or low. *A priori* in aortic disease both arterioles, capillaries and venules might be relatively toneless, and yet, owing to low mean pressure in the arteries, the flow of blood to the skin might be only normal or even subnormal in quantity. In a case of free aortic regurgitation, a skin of normal colour and warmth indicates that the flow of blood through it is normal in amount: but if the mean arterial pressure were below normal in the same case, then there would be strong presumptive evidence that the arterioles were dilated. It is not easy to assess the mean pressure in aortic cases. The systolic pressure is usually raised and the diastolic pressure lowered, often by about equal amounts: but since the pressures of diastole as a whole diverge less from the minimal pressure than the pressures of systole as a whole diverge from the maximal pressure, so it is probable that when the diastolic pressure is lowered by an amount equal to the rise of the systolic pressure, the mean pressure is reduced. Arguing along these lines, we should not necessarily anticipate in a case of aortic disease, in which the tone of capillaries and venules was normal but in which the arterioles were wider than normal, that the colour and temperature of the skin would be higher than normal: we should expect the last only when mean blood pressure was normal or above normal. A skin warmer and more flushed than normal would certainly indicate widened arterioles in the presence of a low mean arterial pressure.

Now the traditional description of skin colour in aortic disease is summed up in the word pallor. This description was written before subacute or chronic infective endocarditis, a disease commonly associated with free aortic regurgitation, was recognised: otherwise it never had been written so. It has for some while been clear to me¹⁵ that aortic regurgitation is a defect in which facial pallor—and it is facial pallor that is understood—does not occur unless it is complicated by infective endocarditis, active rheumatism, or some other recognisable though more occasional cause of anaemia: since I have learned to diagnose the more obscure forms of infective endocarditis, I cannot recall, amongst very many hundred cases of chronic aortic regurgitation, a single instance of unusual pallor of the face, in which that pallor* could reasonably be attributed to low mean pressure in the arteries. The

* I omit from consideration those cases which present pallor as they approach towards the final stages of cardiac failure.

facial colour in those who suffer from uncomplicated regurgitation, uncomplicated in the manner previously described, is normal or it may be heightened. To place this question of facial colour beyond all reasonable doubt I have recently noted it in 24 additional cases of aortic regurgitation in men of different ages. These cases were selected from one point of view only, namely, that they should display a full water-hammer pulse and very high pulse pressure. To summarise these notes, in 9 cases the face was judged to be more flushed than normal, in 2 cases it was intensely flushed, in 12 the colour seemed of natural height. In 1 case only was there pallor, and this was a frank instance of infective endocarditis, proved a month later at post mortem. In an out-patient department especially, the facial colour in cases of aortic regurgitation cases is conspicuous, if it be conspicuous at all, by its redness and by the arterial tint of this redness. It is usual to see spontaneous capillary pulsation in the forehead and cheeks of these standing patients, and spontaneous capillary pulsation is seen only when the part is flushed, at the least in systole. The heightened colour is perhaps less conspicuous in patients long in bed; it varies much in one and the same case from time to time.

So far as warmth of the skin is concerned, that is more difficult to judge; a comparison between a group of aortic cases and a group of control subjects (Appended note C) has shown the average facial temperature to be 1° C. higher in the aortic group. Had the average temperature in the two groups proved equal it would have sufficed for my argument; the higher temperature of the aortic group gives these observations an added significance.

There is a not infrequent type of aortic regurgitation in which the flush is intense and the face and neck are scarlet and hot. The limits of the flush are those of the amyl nitrite reaction, and the patients themselves feel the heat and often the throb of the skin. It is in such that capillary pulsation is seen at its height. In one such case recently observed, the red colour subsided only after many weeks in bed, to reappear after a short period of slow walking exercise; in another it would decline more quickly with rest, namely, in the space of perhaps an hour to appear again without apparent cause. In both these patients the superficial temporal arteries were visible as prominent and tortuous vessels beating violently from the ear almost to the summit of the scalp. In those, of the series of 24 cases, in which the facial colour was noted as higher than normal, it was generally noted also that these arteries were prominent or very prominent, while amongst those in whom the facial colour is stated to have been natural, unusual prominence of the temporal arteries was much less often seen. It is in general true that the flushed countenance associates itself with prominent vessels, though there are not infrequent exceptions, in which one or other of the two fails. These wide and tortuous arteries are usually, and often erroneously, regarded as the products of disease, arteries which have lost their power of elastic recoil. They are common both in young and in elderly cases of free regurgitation, and a simple enquiry proves them capable of changing size. They

shrink, often to invisibility, in response to an ice bag applied for a few minutes; they dilate again readily with heat. In young people, sponging with hot water will often bring forth a prominently tortuous vessel at the temple. In aortic cases, these prominent and pulsating temporal arteries exhibit a recurrent pulse particularly well. Thus, while in free aortic regurgitation there is usually evidence conveyed by warmth and colour that the facial arterioles are dilated, there is often further evidence that the main arteries may be involved simultaneously. It may not be the temporals only; part of the course of the facial artery and also the nasal arteries are not infrequently displayed by their dilatation.

Capillary pulsation in the face is particularly associated, as I have said, with a warm and reddened skin, which being interpreted means relatively wide arterioles. This relation to vaso-dilatation was recently well displayed by a case of free aortic reflux. The following are the relevant observations. A man of 54 years presented himself at the clinic with signs of syphilitic aortitis. Giving a past history of venereal disease at 19 years, he showed clinically and skiagraphically a fusiform aneurism or great dilatation involving both ascending, transverse and descending aorta, and clear signs of moderate regurgitation through the aortic valves. The pulse was a little abrupt in its upstroke, the blood pressure was 180 (systolic) and 110 (diastolic), the pulse rate 90. Both sides of the face were flushed, the right rather more than naturally, the left very distinctly so. The meaning of the greater flush over the left face was not obscure, for the left pupil was much smaller than the right one. Here an arteriolar dilatation, due on the left side to sympathetic paresis, seems indubitable. Over the chin and mucous membrane of the lip capillary pulsation was distinct and seemed equal on the two sides. Over the right cheek, forehead and lobe of ear it was just visible or distinct; over the corresponding parts of the left face it was distinct or vivid. A few venules in the left cheek pulsated, in those of the right pulsation could not be seen. Subsequent investigation (see Appended note E) showed the temperature of the left face to be on the average 1.2°C . higher than that of the right face in this patient.

Cyanosis and arteriolar dilatation. Dilatation of the arterioles leads, other things being equal, to a quicker blood flow through the capillaries and venules of the skin, and tends in consequence to maintain the blood of these small vessels in a more oxygenated state, since less hæmoglobin is reduced by the tissues in its passage through them. Thus arteriolar dilatation is opposed to cyanosis. Several illustrations of this fact have been given. If a normal arm be cyanosed by raising venous pressure in it to 70 mm. Hg. for 3 minutes, the whole arm assumes a more or less deep cyanotic tinge. If a portion of this cyanosed arm is immersed in hot water, the cyanosis vanishes from the immersed part, which becomes bright pink or red in colour; similarly, if the arm is heavily stroked with a blunt point, the region of the

stroke shows red on a bluish background. Congesting a limb to a fixed point is thus a method of displaying areas in which the supplying arterioles are dilated. I have used the method a good deal in cases of free aortic regurgitation with the idea of comparing the depth of cyanosis, so produced, with that similarly produced in the normal subject; hoping thereby to obtain further evidence for or against arteriolar dilatation in these patients. The procedure is to congest the normal arm and that of an aortic case, presenting capillary pulsation in the hand, simultaneously and to the same point, maintaining a pressure of 70 mm. Hg. for 3 minutes, and then comparing the depth of cyanosis in the two arms. To compare the depth of cyanosis is not always an easy matter, since the depth of colour varies much in different parts of the limb; the method is essentially subjective; the comparison is also disturbed because the skin is richer in superficial vessels in some than in others; age probably counts for much; moreover, since the mean pressure in normal and aortic subjects is not necessarily the same, the constant use of 70 mm. congesting pressure is somewhat arbitrary. In general, however, I believe it to be true that congestion of the arm of an aortic case, showing capillary pulsation in the fingers, leads to less skin cyanosis than does similar congestion of a normal arm which shows none. In some cases there is no doubt that this is so, for the arm remains of a pink colour throughout the observation; this is especially the case when capillary pulsation is previously vivid in the hand. In several cases also it has been observed that those portions of the hand which originally showed distinct or vivid pulsation become the least cyanosed when congested artificially. But a few exceptions have been noted, and have remained unexplained, and these have weakened the evidence derived from this source. Although treated as a whole this evidence supports the view that the arterioles are dilated, it is not infrequently indecisive. The arm is not the part in which a state of arterial dilatation is thought to be present in greatest degree; but it is the most suitable to congest. Artificial congestion of the head, in which the chief dilatation is suspected, has not been attempted, but clinical experience may be cited from this standpoint. I have been impressed by the comparative rarity with which cyanosis of the face is seen in free aortic regurgitation, even though such aortic defects are not very uncommonly associated with congestion of the venous system. One patient, seen quite recently, was especially impressive from this point of view. Free regurgitation was present and the veins of the neck were so congested as to project prominently when the patient stood, and were very firm to feel when the patient was recumbent. In neither position was there appreciable cyanosis in any part of the face, but the whole was warm and flushed to an almost bright red colour. The colour, from past experience of similarly congested cases, seemed incompatible with the state of the veins, unless a vasodilatation in the affected area were assumed; the entire face presented a distinct or conspicuous capillary pulsation.

The cumulative evidence proves that capillary pulsation in aortic disease is intimately connected with the state of the arterioles: it also proves that in the areas of skin which show capillary pulsation the arterioles are dilated by comparison to those of skin failing to show pulsation. It further seems clear that in cases in which the mean blood pressure is approximately normal or is below normal, distinct pulsation in the fingers or very distinct pulsation in the face is associated with an absolute dilatation of the corresponding arterioles. It is more accurate to regard capillary pulsation, even in aortic disease, as a sign of arteriolar dilatation than as a sign of high pulse pressure. It may be stated on these grounds and especially from the testimony of skin temperature that the arterioles of the facial skin are customarily widened in aortic disease, sometimes greatly widened. The field primarily selected is a susceptible area, the area which amyl nitrite and emotional blushing influences principally. The arterioles of the upper limb, of the hand especially, share in this dilatation, though with less uniformity and usually in lesser degree. In the foot, evidence of arteriolar dilatation is found relatively infrequently. Often, though not invariably, dilatation of the main arteries supplying the corresponding areas is associated with this widening of the arterioles.

The cause of the limited vasodilatation described remains obscure: to discuss its mechanism, to speak of it as possibly compensatory, would lead us into what, for the moment, would be almost pure speculation.

THE VESSELS INVOLVED IN CLINICAL "CAPILLARY PULSATION."

Usually it has been assumed that "capillary pulsation," as we witness it clinically, is an affair of the capillaries themselves; latterly, however, doubt has arisen, since it has become known that the capillaries are not solely responsible for skin colour, but that the minute venules which collect the capillary blood, and the sub-papillary venous plexus into which the last empty, contribute materially. The capillaries probably contribute in the skin of the hands and feet and in the mucous membrane of the lips; the venules play the largest part in the whiter skin of the limbs and trunk and in the skin of the face. The precise extent to which capillaries on the one hand, and minute venules on the other affect the skin colour in various regions is still uncertain, though it becomes more and more evident that the venules are chiefly responsible. Thinking on these lines, Boas² has suggested that possibly the venules may be largely concerned in producing so-called "capillary pulsation," more especially as he was at first unable to detect pulsation in the capillaries microscopically. Boas was of opinion that pulsation of the capillaries reported by Freeland¹ and Lenhart⁵, Jürgensen¹³ and others²¹, is artificial and due to movement of the capillary bed as a whole. Acting on my suggestion, Sumbal²⁰ was able clearly to display pulsation in the blood-flow of the capillaries themselves in each of 9 cases of aortic regurgitation

examined by him, and he described it in such detail as fully to establish its occurrence. Boas³ has more recently confirmed Sumbal, though maintaining that clinical capillary pulsation may occur when no pulsatile movement is visible in the capillaries, and that pulsation in the capillaries is only seen rarely. I have examined this point extensively, using a Zeiss Greenough binocular microscope and a magnification of 62 diameters, and cannot agree with his findings, never having failed to see pulsatile capillary flow, or pulsatile expansion of the capillary loops, in any area examined microscopically in which pulsation of colour was visible to the naked eye and in which microscopically the blood flow in a reasonable number of capillaries could be detected. Such observations have been undertaken on the mucous membrane of the lips, in the skin of the cheek, of the fingers behind the nail bed and of the arms; in all these the rule has held good. Boas states that he has failed to detect pulsation in the capillaries of this nail bed in all of 8 cases of aortic disease examined, though care was taken to examine the skin while the background was flushing and paling. Sumbal saw it in several cases of his series, and more recently I have not failed to see it unmistakably in any case, providing that the field of observation changed its depth of colour in systole. It seems to me that Boas has failed to detect the pulsation in many instances in which it was actually occurring.

It is to be said at once that pulsation in the capillaries is not always easy to detect, often requiring the closest attention and prolonged examination. No statement that pulsation of capillary contents is absent is safe, at the least until the flow is clearly seen and determined to be uniform; thus, in the skin vessels of the arm, as usually examined by placing a drop of cedar wood oil or other highly refractile oil on the skin, it is only the tops of comparatively few of the existing capillary loops which are actually seen, and in these it is rarely possible to view the actual blood flow. In such it is quite impossible to exclude pulsation of the contents. When it is at first thought absent, it often may be displayed by particular attention to method. Frequently a much deeper view of the skin may be obtained by first dehydrating the skin with absolute alcohol, applying cedar wood oil subsequently. In the case of the arm this often suffices to bring the afferent and efferent limbs of deeper capillaries into view and to display the flow in them. Spontaneous capillary pulsation in the skin of the arm is a very rare event and, as it is beside the present point to discuss whether pulsation in the capillaries occurs where clinical pulsation is not visible—a point too frequently neglected in the reports of previous workers—some means of inducing it in the forearm is required. This may be accomplished by stroking the arm or rubbing it; but such pulsation is too fleeting to be of much value. An effective method is to apply a blister, removing the horny layer completely, and to maintain the surface so exposed greased when not under observation. This method gives an unrivalled view of the vessels and circulation in the skin; it is suitable for studying the anatomy of the skin vessels, but is unsuitable for studying their physiology, owing to the

preliminary, though mild inflammatory reaction. It is eminently suited to the study of capillary pulsation, and I have used it frequently. The blister produces the required redness of the area affected, clinical pulsation persisting for several days and after the flush in the surrounding skin has subsided.

In instances of faint clinical pulsation, it may be necessary to search numerous capillaries before the pulsation is seen; in many there may be stasis, temporary or permanent and consequent upon the pressure exerted; in others there may be what is apparently uniform flow; in yet others, may be isolated or in groups, pulsation may be occurring quietly or vigorously. In capillaries in which the flow is very rapid, and this is frequent, it is well-nigh impossible to exclude pulsatile flow. In examining such it is necessary to alter the pressure exerted upon them and to re-examine the movements of the blood column when this is restrained. In the skin of the cheek very few of the existing capillaries can be seen sufficiently clearly to determine flow, and in this area therefore the question cannot always be settled, though here again I have frequently seen pulsation in isolated capillaries. There is little or no doubt in my mind that the clinical pulsation of aortic disease is always associated with pulsatile flow in the capillaries, wherever it may occur. The detailed change in the vessels described by Sumbal I can fully confirm, and can add that, by suitably grading the pressure in cases of vivid pulsation of the fingers, I have repeatedly seen every capillary loop in a wide field springing into view with each pulse of the arteries, to disappear almost completely or entirely in diastole. In such circumstances, where as in the fingers the capillaries are numerous and densely set, the contribution of the capillaries to clinical pulsation must be material, particularly since these are the most superficial blood vessels of the skin and hence least veiled by intervening tissue. But I am in agreement with Boas that clinical pulsation does not arise solely from the capillary factor, and am able to substantiate his suggestion that the venules contribute, having actually witnessed pulsation in these on many occasions.

Involvement of veins and venules in the pulsation.

In his classical experiments on the submaxillary gland, Claude Bernard¹ described how on stimulating its nerve, the blood issuing from the gland increases in quantity and changes its colour from black to red: it spurts from the cut vein in gushes which synchronise with the pulse. This pulsation in flow is probably, though it is not necessarily, transmitted from arterioles to veins via the capillaries; in an encapsulated gland each arterial pulsation will raise the intraglandular pressure and force blood out of veins. A similar hesitation occurs in finally interpreting Quincke's observation¹⁷; he observed centripetal pulsation in the veins of his own hand when the last was much swollen by heat.

Pulsation of veins in aortic disease is most readily to be seen in the small venules lying superficially in the skin of the cheeks and nose ; these veins swell in systole. Where, as in cases of free aortic regurgitation, the colour of the face changes spontaneously with each pulse beat or pulsates vividly on pressure, pulsation in these small venules, themselves placed under suitable pressure though sometimes without pressure, can almost always be recognised both macroscopically and microscopically. I have seen this phenomenon in a large number of aortic cases, but its meaning cannot often be interpreted decisively. The venule swells in systole. Under the microscope the direction in which the current flows in these veins is often though not always determinable. When determined I have seen no exception to the rule that the sharp pulsatile movement is in the direction of the current, suggesting its peripheral origin : in a few instances capillaries have been traced into such venules and systolic pulsation in the last has been traced into the venule itself. Usually, however, the tributaries of these venules cannot be clearly traced, and it is often seen that there are large vertical channels of anastomosis with vessels lying deeper ; pulsation may be seen in the mouths of these anastomoses, and sometimes there is the impression that blood is forced towards the surface from deeper parts during systole. If this is so, it may be a displacement phenomenon, comparable to that which has been suggested as possible in the case of the submaxillary gland. But I am inclined to think it is not so, but that it is but an impression gained from swelling of the vein and rhythmic darkening of the mouth of the vertical vessel. The conjunctival vessels have also been studied in a number of patients because, on the background of the white sclerotic, the flow of blood in all the small vessels is seen to great advantage. Not much, however, has been gained by this study. In most of the venules the flow is apparently uniform ; but pulsation on the eyeball has not been witnessed macroscopically. In a few instances pulsatile blood flow has been seen distinctly in capillaries, transmitted from minute arterioles supplying them, and on occasion such pulsation has extended a little way into a collecting venule. Once or twice pulsation has been seen in a larger venule and then always in the direction of the current. With these few exceptions the observations have been unconvincing however, they are at all times trying to the observer, since it is almost impossible to eliminate the little jerk of the whole field with each beat of the heart, and this jerk comes at a critical instant, when attention must be focussed most sharply on the events inside the vessels.

To display pulsation in the smallest veins in areas showing the clinical capillary pulse, the blister method is the most reliable : it has been used on the forearm and in the skin directly above the nail bed. The following observations are sufficiently illustrative.

D. L., a man of 27 years, suffered from enlargement of the heart, free aortic regurgitation and subacute infective endocarditis, from which he subsequently died. The blood pressures in the arm were 132 (systolic) and 55 (diastolic). The palm of the hand, when held up, presented spontaneous

capillary pulsation of an unusually vivid kind; on pressing a glass plate against the pads or sides of the fingers, or against the skin above the nail bed, vivid capillary pulsation was to be seen; at certain pressures in the last area the skin changed rhythmically from a full red to white. Pulsation in the digital arteries was forcible. The skin at the base of the nail of the ring finger was blistered and a few hours afterwards the blister rose. The skin covering the blister extended as far as the nail; it was removed and the underlying layer cleaned and anointed with liquid paraffin. This area was examined on the same day and on the 3rd day; similar events being seen on both occasions. The following account is abstracted from the notes. To the naked eye the blistered area has the redness usual to a raw surface and, uncompressed, faint pulsation is visible in it. Under the microscope the horizontal capillary loops at the base of the nail are fully displayed, as are the short collecting venules and considerable portions of the larger venules into which these open. The arterioles, each supplying one or more capillary loops, are also clearly to be distinguished (see Fig. 4). The blood is seen to pulsate in the capillaries and here and there in the short collecting venules, but the current is rapid and the events difficult to define accurately. A glass slide is fixed to exert a very little pressure on the area immediately behind this, and to produce a small area of pallor. Macroscopic pulsation at once becomes vivid. On examining this pulsation microscopically the loops of capillaries are seen to run almost vertically, both the afferent and efferent limbs of all these capillary loops swell up at each systole and most of them disappear entirely in diastole; when the capillaries flush, the network of venules deep to them springs into view, disappearing at each diastole or becoming indistinct. The background of this venous network does not seem to change its colour. Examining, under like pressure, the vessels at the immediate base of the nail, similar events are witnessed, though here only a proportion of the capillaries disappear from view in diastole. It is in this region of the skin that both the arteriole and venous connections of the capillary loops are most clearly distinguishable, and in all parts of the visible system, of which Fig. 4 depicts a portion, the blood current is discernible without break. Blood is seen to pulse up the arteriole, throughout the whole loop and to descend and distend the short collecting venules and the larger venules into which these open at each systole. When the pressure has been a little increased, the larger venules and portions of the small collecting venules disappear and the blood now pulsates from the arterioles into the capillary loops (afferent and efferent limbs), but only a little circulates through them. If the pressure is released again the circulation once more becomes active, and jets of blood force their way further and further down the short collecting venules into the larger venules, which simultaneously fill and pulsate. Pulsation may be seen in the collecting venules when it is not to be seen in the larger venules into which the latter open: it is never seen in the larger venules when absent in the corresponding collecting venules. The pulsation is systolic in all parts of the system and is invariably in the natural direction

of the blood flow. The pulse is a single one transmitted from arteriole, through capillary loops into venules. When the pressure of the glass is increased so as to obliterate the larger venules, the blood current for a short while becomes reversed in the capillary loops, which continue to pulsate; but the pulsation is now directed against the flow, and is confined to the arteriole and capillary loop. A small portion of a field is accurately depicted in Fig. 4, the arrows showing the natural direction of the blood current. Similar events were watched in other parts of the same nail bed.

G. R., a man of 49 years, suffered from syphilitic aortitis, enlargement of the heart, and free regurgitation at the aortic valve. The brachial blood pressures were 210 (systolic) and 70 (diastolic). Capillary pulsation was visible to the naked eye on pressing a glass sheet on various parts of the palm of the hand, in the pads of the fingers and at the base of the nail. On stroking the forearm firmly, pulsation appeared in the red line subsequently developed there. The forearm was blistered over a small area, the blister skin removed and the skin examined on the 3rd day under liquid paraffin. In the skin outside the blistered area, the tops of widely separated capillary loops could be seen, and no more than this. On turning to the bare area, a clear view was obtained of the whole capillary system with its collecting venules and portions of the subpapillary venous plexus; other portions of the subpapillary plexus were more dimly seen (Fig. 5). The arterioles supplying the capillaries were thread-like. In the figure the vessels are shown in different shades, the darkest representing the most superficial and the lightest the deepest vessel. Of the vascular system here represented, only the two dark and adjacent loops in the lower and central portion of the figure would have been visible in the unblistered skin; the remaining capillaries, taking a deeper course, and running more parallel to the skin surface, would also have remained hidden, as would the collecting venules.* Capillaries lying deeper still and seemingly on a level with the collecting venules occurred here and there, as for example the small group of fine vessels emerging from the arteriole to the extreme left in Fig. 5. The natural direction of blood flow in the vessels is indicated with arrows in Fig. 5 wherever it could be recognised unmistakably. The deepest visible vessels were hazy and in these the direction of flow could not be determined, neither could pulsation be seen in them or in the background. In all the remainder of this system pulsation of the blood contents was witnessed under a pressure sufficient to produce slight paling of the skin and slight pulsation macroscopically. As in the preparation last described, but in the present one especially, the velocity of flow in the arterioles greatly exceeded that in the capillaries and venules. The pulsation was always transmitted in the direction of natural flow and, decreasing in magnitude as it travelled through capillaries and collecting venules, was lost to vision in these or in the plexus veins. In this preparation and in others pulsation in the venules has been

* In some forearms they are dimly visible.

seen from time to time and under certain pressures, while in overlying capillaries flow has been absent or seemingly uniform; but these overlying capillaries were in such cases not the sole tributaries of the underlying venules; in examples of this kind the pulsation in the venules has also been in the natural direction of blood flow and, when such venules could be traced fully to their sources, pulsating capillaries have always been found.

Recently in a patient having free aortic regurgitation and a thin skin above the nail bed, by first soaking the skin with alcohol and subsequently applying cedar wood oil, the main events here described have been seen also in the unblistered finger.

Thus, there is no doubt from observations on the cheek and skin of the limbs that "capillary pulsation" is contributed to by the venules, and that often the part played by the venules is no small one; especially is this the case, as Boas has supposed, in the skin areas where capillaries are relatively scanty, as in the cheek and forearm; in the last instance, however, it is to be stated that numerically the capillaries in the skin of the forearm are under-estimated in viewing these simply by Lombard's method. The capillaries themselves play a larger part in producing the phenomenon in the lips and in those skin areas, such as the ventral surface of the hands, which are ridged.

There seems to be no doubt that pulsation such as can be seen in the venules of the hand and arm, is a pulsation transmitted to the veins via the capillaries. If, as has been supposed, pulsation may be transmitted to the venules through the arteriole-venule anastomoses described in the deeper layers of the skin by Suequet¹⁹, Hoyer¹² and Grosser¹⁰, it would be expected that pulsation in a direction opposite to the blood stream in the venules, and pulsation confined to the efferent side of the capillary loops, would occur. Such has never been seen, and my experiences as a whole are manifestly opposed to the supposition that capillary pulsation is conveyed from the veins to capillaries. The anastomoses in question are known definitely to exist in the skin of the hand and foot only,* and in these they are confined or almost confined to the ends of the digits. Capillary pulsation can occur in any part of the skin of the body. I conclude, therefore, that these anastomoses play no part in inducing clinical capillary pulsation.

Capillary pulsation in the heated skin of normal subjects.

If the nail bed of a young normal subject is exposed to an unguarded light, and warmed until local throbbing is felt by the subject and pulsation is visible on pressing the skin, the microscope reveals a pulsatile blood flow in the capillaries which is in every detail similar to though less extensive than that seen in aortic disease.

* Suequet described them in many other parts of the body, but later workers have failed to confirm him.

Clinical pulsation as a transmitted phenomenon.

Jürgensen¹⁵ states that clinical capillary pulsation is seen in many cases of arteriosclerosis exhibiting high blood pressure, but that in none of these could he observe pulsation in the capillary flow microscopically. He believes apparently that the clinical pulsation is in these transmitted from the digital arteries and arterioles, and is due to movement of the whole field. The same idea has been expressed in regard to instances of clinical pulsation in aortic disease by several workers^{2 & 8}. It appears to me that pulsation so arising would consist of a paling of the capillaries and venules in systole, these vessels being squeezed between the expanding arteries and arterioles and the glass: I have never seen paling, in systole, and confess to scepticism that clinical capillary pulsation ever arises in this way. I have examined the lip or finger nail bed in two cases of arterial disease and high blood pressure such as Jürgensen described; these cases presented slight but definite clinical pulsation, and in both pulsation of the capillary flow was quite distinct. There appears to be no sufficient basis at present upon which to divide cases of clinical capillary pulsation into two distinct classes; and the evidence, as it now stands, seems to warrant us in concluding that in all instances of clinical capillary pulsation the capillaries are directly involved and that the rhythmical change of colour, seen macroscopically, is always due to pulsatile flow in the minute vessels of the skin, involving always the capillaries, and perhaps always involving through these the collecting venules and the venules of the subpapillary plexus.

APPENDED NOTES ON SKIN TEMPERATURE.

(OBSERVATIONS IN COLLABORATION WITH DR. E. P. WOLF.)

A. Method. To test skin temperatures we have used a simple form of thermo-electric couple. This was made for us by Professor A. V. Hill, to whom we are also indebted for hints as to its proper use. Each junction consists of a circular plate of silver foil, 6 mm. in diameter; to this plate two fine and insulated wires, one of copper and the other of constantan, are soldered and the plate is cemented to the flat end of a vulcanite rod (Fig. 1); the two wires are carried up the rod and bound to it with silk, the whole junction being subsequently coated with insulating varnish. The vulcanite rod serves as a handle. The two junctions are connected together and to a mirror galvanometer of suitable sensitivity. One junction is kept at a constant temperature (at about 30°C.) in a thermos flask, the other is applied to the skin which it is desired to test (Fig. 1). The deflection of the galvanometer is read and the reading subsequently converted to centigrade temperature by calibrating the instrument. We have used the galvanometer at such sensitivities as yield deflections of either 6 or 18 scale divisions to each 1° of centigrade temperature.

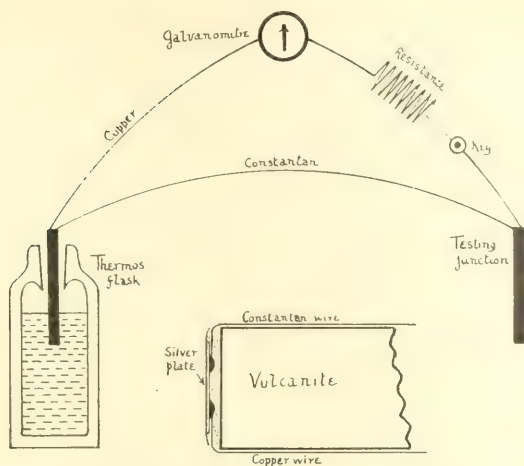


Fig. 1. A diagram showing the general arrangement of the thermal couple when in use, and a diagrammatic section of one thermal junction (enlarged).

When the testing junction at room temperature is placed on one small area of warm skin, the spot of light shows a large and rapid excursion occupying 5 or 6 seconds; subsequently the spot of light moves much more slowly in the same direction and finally becomes stationary in about 15 or 20 seconds. The time of the first rapid deflection is controlled by the period of the mirror galvanometer, and diminishes as the excursion is less. The slower after-movement is due to warming up of the skin under the contact. This warming up of the skin is not due in any considerable measure to covering of the skin and a consequent retention of heat, but to the fact that when the silver plate at room temperature is placed on the warm skin it cools the skin, and the subsequent change is due to the skin returning to its original temperature. This can be shown by moving the contact, when the beam of light has attained its final and stationary position, to an adjacent skin area; in general the same final reading is then obtained and is obtained almost immediately. To obtain accurate and quick readings, the junction should be in contact with the tested skin for as short intervals as possible; the time of contact is controlled by the duration of the beam's swing; by shortening the time of contact, change in skin temperature, due either to covering of the skin, or to the slight pressure of contact interfering with the superficial vessels, is avoided. The procedure, therefore, is fully to warm the contact on an adjacent area or areas of skin, and to move it quickly to its final position. The actual reading is then obtained in 1 or 2 seconds.

B. Skin temperature and degree of capillary pulsation related in aortic disease. The temperatures of the face, hands and foot have been taken in 7 patients suffering from free aortic regurgitation. These patients came in moderately cold weather from airy wards or from an out-patient department, having to pass through the open air before arriving at the examination room, the temperature of which was at or about 20°C.. On arrival, parts of the exposed skin were always cold or cool to the touch and remained so for 5 or 10 minutes, before becoming warm. The temperature readings were taken at once and while the skin presented different temperatures in different places. The details of all these examinations need not be given; the following is an illustration. A man of 42 years, suffering from free aortic regurgitation, was found to have a blood pressure of 170 (systolic) and 85 (diastolic); his rectal temperature was 37.6°C.. Table IV summarises the observations on his skin, and shows clearly how the intensity of pulsation increases as we pass from a colder to a hotter skin area.

TABLE IV (No. 4 of TABLE V).

	Capillary pulse.	Temp. (cent.)
Lobe of right ear	none	23.4°
Bed of finger nail	none	26.8°
Side of nose	none	26.8°
Pad of finger	none	28.1
Pad of big toe	none	28.1°
Heel	none	28.5°
Right cheek	slight	28.9°
Pad of big toe after massage	distinct	31.2°
Forehead	very distinct	32.0°
	(spontaneous)	
Left cheek	very distinct	32.6°
	(spontaneous)	
Right cheek (later)	very distinct	33.6°
	(spontaneous)	
Lower lip, facial mucous membrane	vivid	34.7°
Lobe of right ear after massage	vivid	35.5°

A summary of the observations upon the 7 cases is given in Table V. The skin areas are grouped in this table, according to the degree of pulsation shown in them and are related to temperature. The average temperature values (in brackets) show the relation with particular clearness. The maximal and minimal readings also display the relation, though discrepancies occur here and there. The discrepancies, most of which are minor discrepancies, may arise in one of several ways: there is often difficulty in judging the grade of pulsation sufficiently closely to class it accurately; the skin covering different parts of the body is compared and the temperature at which capillary pulsation first appears is not the same for all

TABLE V.

Temperatures (centigrade) of skin of face, hand and foot and degree of capillary pulsation compared in 7 autic cases.

<i>Capillary pulsation.</i>	1.	2.	3.	4.	5.	6.	7.
Absent	25.3—25.8 (25.5 ± 2)*	29.4—31.4 (30.1 ± 5)	30.9 (30.9)	23.4—28.5 (26.9 ± 6)	22.5—26.5 (24.5 ± 4)	23.0—27.3 (25.8 ± 3)	22.1—23.1 (22.6 ± 2)
Slight	28.8—30.6 (29.6 ± 3)	29.9—31.7 (30.7 ± 7)		28.9 (28.9)	28.3—29.7 (28.8 ± 3)	26.3—27.6 (27.1 ± 3)	28.2—34.0 (31.6 ± 6)
Distinct	30.4—31.7 (31.3 ± 7)	31.1—32.6 (32.3 ± 2)	31.2 (31.2)	33.3 (33.3)		32.0—34.5 (33.2 ± 4)
V. distinct	29.8—32.6 (31.4 ± 3)	33.4 (33.4)	31.5—34.1 (33.0 ± 4)	32.0—33.6 (32.7 ± 3)	33.6—34.1 (33.8 ± 4)	30.9—32.1 (31.5 ± 3)	32.5—34.7 (33.7 ± 4)
Vivid	32.5—33.4 (32.8 ± 4)	32.9 (32.9)	34.1—35.2 (34.5 ± 5)	35.5 (35.5)		33.9—35.3 (34.6 ± 2)	33.2—34.5 (33.9 ± 4)
Rectal temp.†	37.5	37.2°	37.1	37.6°	37.4°	37.3°	37.2°
Blood pressure	188/45	134/56	215/80	170/80	164/80	176/65	160/76
Room temp.	21	21°	21°	19	22°	21°	20.5
Air	28	37	49	42	56	47	43

* The maximal and minimal temperature readings, and the average temperature and number of areas examined (the last two in brackets).

† In these and all other similar observations the same thermometer has been used as was employed in calibrating the thermal couple.

parts;* and lastly, pulsation when distinct is sometimes confined to a smaller areas than that covered by the testing plate of metal. Grouping these cases of free aortic regurgitation together and speaking of the skin of the face, fingers and sole of the foot, the following broad conclusions may be drawn. Capillary pulsation is rarely seen in the skin if its temperature is below $28^{\circ}\text{C}.$. Slight pulsation is usually found when the temperature lies between about 28° and 30° ; distinct or very distinct pulsation when it lies between about 31° and 33° ; and very distinct or vivid pulsation when it lies between about 33° and 35° .

C. Skin temperatures of normals and aortic cases compared. A comparison of absolute skin temperature in different individuals is somewhat more precarious than is a comparison of the temperature of different skin areas in the same individual. It is clearly of importance in attempting the first to maintain external conditions as constant as possible. A group of male aortic cases and a group of male controls has been examined in a room kept at a temperature of $17^{\circ}\text{C}.$; the room has been well ventilated, but the well-clad patient has been placed out of draught and maintained lying until the readings of skin temperatures have become constant. One or more aortic cases and one or more controls have been examined at a sitting and under similar conditions. Readings have been taken from the forehead, both cheeks, the chin and the side of the nose, and this group of readings averaged for comparison. Readings of the lip and rectal temperatures have been added and are shown in Table VI. These aortic cases were selected as examples in which mean blood pressure is judged to have been near or below normal and they are arranged in the approximate order in which they displayed capillary pulsation in the facial skin as a whole. These readings may be compared with those shown by the group of controls (Table VII). The average rectal temperature proves to be the same in the two groups: the average temperature of the facial skin is $1^{\circ}\text{C}.$ higher in the aortic than in the control group; the figures being 32.9° and 31.9° , respectively. A rise of facial skin temperature of 1° from an original level of 31.9° in a given patient is apparently brought about only by a conspicuous increase of blood flow (see sections G, H and I). Perhaps the most correct view of the difference is obtained by stating that in the control group the facial skin falls short of rectal temperature by $5.3^{\circ}\text{C}.$, while in the aortic cases the difference is narrowed to $4.3^{\circ}\text{C}.$. The temperature of the mucous membrane of the lower lip in the two series shows an even more notable difference, being 4.8° below the rectal temperature in the controls and only 2.5° below in the aortic cases. We realise that a comparison between two

* Not infrequently there is a discrepancy between the skin of forehead and cheek; often the skin of the forehead is slightly warmer than that of the cheeks, yet in these circumstances the cheeks may often show pulsation more clearly than does the forehead. The cheeks are usually redder than the forehead, the venules, which participate in the pulsation, being more prominent. The arrangement of the minute vessels evidently influences the degree of pulsation.

TABLE VI.

Pre-aortic reorganization.

No.	1.	2.	3.	4.	5.	6.	7.	8.	9.	Averages.
Age	...	28	41	30	37	30	43	38	42	
Lip	...	35.4	35.2	35.3	35.1	34.7	34.8	33.9	33.2	34.7
Forehead	...	33.3	33.8	33.2	32.2	32.9	33.3	32.4	33.2	33.1
Cheeks	...	33.3	33.4	34.3	32.4	31.3	32.6	32.8	33.3	33.0
Chin	...	33.9	33.4	32.3	32.8	33.2	33.1	31.2	32.9	33.0
Nose	...	33.3	31.6	32.2	33.2	33.0	32.4	32.0	30.0	32.3
Average	...	33.4	33.1	33.0	32.6	32.6	32.8	32.1	32.4	32.9
Rectal	...	37.2	37.6	37.3	37.5	36.7	36.9	37.6	37.3	37.2
Rectal minus average	...	3.4	4.5	4.3	4.9	4.1	4.1	5.5	4.9	4.3
B. P.	...	100.45	156.58	105.50	142.43	132.45	140.54	164.60	145.65	
C. P.	...	very distinct	sl. to vivid	none to vivid	distinct to v. distinct	distinct to v. distinct	distinct to v. distinct	0 to v. distinct	0 to v. distinct	
Room	...	17	16.9	17.3	17.2	16.8	17	17	17	

TABLES VII.
6 healthy controls.

No. ...	1.	2.	3.	4.	5.	6.	Averages.
Age ...	35	47	42	38	33	62	
Lip ...	34.1°	33.0°	34.7°	33.2°	34.2°	34.8°	32.4°
Forehead ...	31.6°	31.4°	33.6°	32.0°	33.1°	32.8°	32.4°
Cheeks ...	31.3°	29.7°	33.5°	32.2°	33.3°	32.2°	32.2°
Chin ...	32.5°	30.8°	32.6°	32.3°	33.5°	33.0°	32.5°
Nose ...	31.8°	26.7°	32.1°	28.9°	33.0°	31.4°	30.6°
Average ...	31.8°	29.6°	32.9°	31.4°	33.2°	32.4°	31.9°
Rectal ...	37.2°	37.2°	37.0°	36.8°	37.6°	37.2°	37.2°
Rectal minus average	5.4°	7.6°	4.1°	5.4°	4.4°	4.8°	5.3°
B. P. ...	130/95	154/108	128/88	96 ?	150/90	136/95	
C. P. ...	none to distinct	none to distinct	none to slight	none to slight	none to slight	none to slight	
Room ...	17°	17°	17°	16.8°	16.8°	17°	

groups of subjects is necessarily somewhat precarious;* yet in view of the extent of the differences in temperature, and in view of the fact that in those aortic cases which showed the most conspicuous pulsation the temperatures of the face were in general higher, as is evident in the table, we regard the observations as decidedly significant, and indicative of an enhanced blood flow.

D. Skin temperature in general erythema of face and neck. In an earlier part of this paper a young patient is described (page 158), who exhibited a bright flush over the face and neck; though the blood pressures were normal, this flushed skin presented a very distinct capillary pulsation. This patient and another very similar instance, a man of 48 years, have been examined under precisely the same conditions as have the groups previously described. In these two cases the average facial temperatures were 34.4° and 34.1°, respectively (see Table VIII); they are amongst the highest values we have as yet seen: in one of these cases the temperature of the lip fell only 1.8° below the rectal temperature. The blood pressures of these two cases were normal, and the temperature values obtained can be explained only by supposing an extremely active blood flow to the skin as a result of conspicuous arteriolar dilatation.

* In two similar series of cases examined at room temperature of 20-21°C. we were unable to find any appreciable difference between the facial temperature of aortic cases and controls. We discarded these results because at this relatively high temperature capillary pulsation was too distinct in the controls to make the comparison valuable.

TABLE VIII.
Facial erythema (2 cases).

No.	1.	2.
Age	29	48
Lip	34.8°	35.5°
Forehead	34.3°	34.0°
Cheeks... ..	34.4°	35.0°
Chin	34.7°	33.5°
Nose	34.1°	33.8°
Average	34.4°	34.1
Rectal	37.3°	37.3°
Rectal minus average ...	2.9°	3.2°
B. P.	138/88	136/95
C. P.	distinct to very distinct	distinct to very distinct
Room	16.7	16.0

E. Skin temperature and capillary pulsation in a case of left cervical sympathetic palsy. The patient described on page 169 has been re-examined at a later date with a view to determining the facial temperatures and correlating these with the degree of capillary pulsation. On this day, however, the difference in the size of the pupils, though distinct, was less conspicuous than on the former occasion. The following table sums up observations on symmetrical areas of his facial skin and mucous membrane :—

TABLE IX.
Left cervical sympathetic palsy.

	Left side.		Right side.	
	Temperature.	Capillary pulsation.	Temperature.	Capillary pulsation.
Lip (angle)	36.5	vivid	34.9°	vivid
Forehead	34.7°	distinct	33.5°	slight
Cheek	34.4°	v. distinct	32.8°	slight to distinct
Nose	34.0°	v. distinct	32.2°	slight
Side of chin	34.4	distinct	33.4°	slight
Lobe of ear... ..	35.3°	v. distinct	35.2°	distinct
Temple	34.5°	v. distinct	33.4°	slight
Upper eyelid	34.2°	slight to distinct	32.8°	slight
Averages	34.7°		33.5°	
Rectal temperature	37.6°	Room temperature 17°		
Blood pressure ...	174 (systolic) 110 (diastolic)			

The average temperature of the facial skin on the left proved to be 34.7° , and on the right 33.5° , a difference of $1.2^{\circ}\text{C}.$ The degree of capillary pulsation was always greater in the left than in the corresponding areas of the right skin. No difference in degree was noticeable, however, in the pulsation of the lower lip; it was vivid on both sides at the angle of the mouth, although the temperature difference in the same areas was 1.6° .

The average temperature of the left face was within 2.9° of the rectal temperature, that of the lip was within 1.1° of the rectal temperature. These values are very similar to those found in the cases of facial erythema described in the last note. They are probably compatible with a full, or almost full, dilatation of the skin arterioles.

F. Temperature of local lesions. Reference has been made to the appearance of capillary pulsation or of an enhanced pulsation in local lesions of the skin, such as infected cuts, acne pustules, herpes labialis, etc.. We have thought it worth while to compare the temperature of such skin areas with that of the immediately surrounding skin. The results are expressed in the following table :—

TABLE X.

Subject.	Age.	Lesion.	Site.	Average temperatures.			Capillary pulsation.
				Affected skin.	Unaffected skin.	Difference.	
Normal	20	acne	lip	35.6	35.1°	0.5°	Vivid in lesion, distinct in surrounding skin.
Normal	20	acne	chin	34.2°	33.7°	0.5°	Distinct in lesion, sl. in surrounding skin.
Aortic	30	small infected cut.	chin	33.0°	32.3°	0.7°	Vivid in lesion, none in surrounding skin.
Aortic	46	acne	neck	32.8	32.4°	0.4	Vivid in lesion, sl. in surrounding skin.
Aortic	41	cut	cheek	33.4°	32.3°	1.1°	V. vivid in lesion, sl. in surrounding skin.
Aortic	39	acne	neck	32.4°	31.9°	0.5°	Vivid in lesion, none in surrounding skin.

These observations were made on cases at room temperatures varying up to $21^{\circ}\text{C}.$, and the readings of different cases are not comparable with each other. Rectal temperatures were not taken.

6. *Temperature rise in urticaria factitia.* The vascular factors involved in dermatographic wheals have been described in a preceding article in this number of the Journal. It is known that the arterioles become dilated in the area of skin stroked, and that the surrounding flush is due to this widening of the vessels. In that article it was judged that the blood flow to skin, on which stroking produces a full wheal in 3 minutes, must be increased many times above normal. Because the wheal and the surrounding erythema present capillary pulsation, and because in some instances of this reaction the arteriolar dilatation is probably as great as it ever is in the human skin, we have been interested in ascertaining the actual rise of temperature. It has been studied in three separate cases, and the results have been very uniform. The skin,

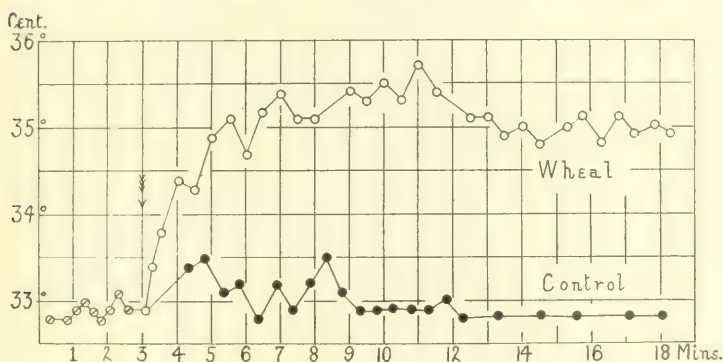


Fig. 2 A chart showing the change in temperature of the skin after stroking it heavily. From a case of urticaria factitia. Rectal temperature 37.6°. The divided circles represent the temperature of the skin of the back before stroking and were taken in part from the area to be stroked and in part from that subsequently used as the control area. The arrow indicates the time of stroking and the plain and black circles represent the subsequent temperature of the skin immediately bordering the line of stroke and of the control skin, respectively.

usually that of the back, has been exposed for some while to a steady room temperature, and repeated readings taken from the area to be stroked, and from a symmetrical area of skin which has subsequently been used for control readings. When the readings are found to be constant, and similar on the two sides of the body, one area is firmly stroked, and regular readings are continued over the line of stroke and over the control area of skin. The rise of temperature in the stroked skin begins about 15-30 seconds after the stroke, and shortly after reddening is first seen: the rise continues for about 2.5 to 6 minutes, until it reaches a point about 1.5° to 2.5° above the original level (the original level being 32°-33°); the temperature curve then runs as a plateau which subsequently declines as the redness of the skin subsides (Fig. 2). The lines of temperature charted are those of the skin

immediately bordering the stroke (that which after stroking becomes brightly flushed and borders the wheal) and the temperature of the control area of skin. Repeated comparison of the temperatures of the wheal itself and the immediately surrounding skin at various stages of the reaction have shown no appreciable or constant difference; that is so even if the wheal proper has passed through its red stage and has become pale.

H. Rise of skin temperature on closing an arterio-venous anastomosis. In a previous article¹⁶ a case of arterio-venous anastomosis has been described (as *Case 1*) in which measurement showed the blood flow to arm and leg to be increased by approximately 100% on closing the femoral artery leading to the anastomosis. We have used this case in a first attempt to obtain a numerical idea of the relation between increased blood flow to the skin and the associated rise of skin temperature. The observations have been made repeatedly upon the skin of the hand and upon the skin of the cheek. In making these observations the thermal junction is not held continuously over one area, but is moved every few seconds in steps around a small circle of skin, readings being taken at each 15 seconds.

The cheek. The temperature of this skin being at a constant level, the femoral artery was occluded. The skin temperature began to rise within about 15-30 seconds of the compression and continued to do so steadily for about 2 to 2½ minutes. The total rise was approximately $\frac{3}{4}$ to 1°C. On releasing the anastomosis a decline occurred occupying about 2 minutes, when the original skin temperature was resumed.

The palm of the hand. Similar curves were obtained, though the rise of temperature was less, being usually 0.4° or 0.5°, and on one occasion 0.8°.

The curves of cheek and hand are exemplified in a chart (Fig. 3). The top curve (cheek) shows a rise from about 33.7°, to 34.4°, the bottom curve (hand) from about 33.0° to 33.4°, with corresponding subsequent falls. A measurement of blood flow to a limb on the same day showed a rise of approximately 100% on closing the anastomosis. This would apparently correspond to a rise of temperature of about 0.5° (from say 33°), if we take the arm curve for comparison and assume that the increased flow is evenly distributed to the skin and muscles, etc., of the limb. If we assume that the blood flow to the face—of which we have no actual measure—is increased to the same and to no greater extent, a 100% increase would correspond to a rise of almost 1°. The first comparison is the more legitimate; and this suggests that a rise of 2° in the skin temperature on stroking in an urticarial subject corresponds to at the very least a four-fold blood flow; we say at the very least, because the rise should in reality be read in terms of the extent to which the rectal-skin temperature difference is diminished. This estimate, drawn as it is from a single case, in which increased blood flow and

temperature rise have been measured, may not be pressed too hard: but in so far as it goes it is not far out of harmony with estimates derived from other sources.

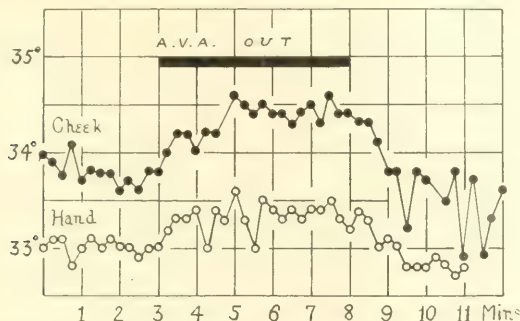


FIG. 3. A chart showing the effect of closing the artery leading to an anastomosis of the superficial femoral artery and vein (*A.V.A. out*) upon the temperature of the cheek and palm, and of the hand. The two observations were made separately, but have been charted together, the femoral artery being compressed and occluded on both occasions for exactly five minutes. It is to be noted that, although the increased and decreased blood flows to the skin begin abruptly, neither the rise nor fall of temperature is completed under two minutes.

I. General note. It has been seen that in room temperature of 17° the average facial skin temperature of aortic cases often approaches the rectal temperature within about 4.0° . In normal people the approach is to about 5.0° . In bright erythema of the face (Table VIII) the difference falls to 3.0° ; and a similar difference has been found in a case of cervical sympathetic paralysis. If we subtract 1° from each of these values, the corresponding differences in temperature between rectum and lip are obtained.* Using the values quite broadly we may say that starting at the normal facial skin temperature of 32° (with rectal temperature 37°), a rise of 2° or an actual temperature of 34° probably represents a full, or an almost full, vasodilatation: this is seen in the flush of urticaria and in bright erythema of the face. A rise of 1° (to 33°) represents, therefore, a considerable though partial vasodilatation; the last has been found in the group of aortic cases (Table VI). It would appear from these values that the degree of vasodilatation found in the aortic cases is by no means negligible. It is, perhaps, the more significant, seeing that in these patients the mean blood pressures were possibly or probably below normal in many instances, though this might

* It is to be stated that the dry mucous membrane of the lip and not that within the buccal cavity has been used.

be held to affect rectal temperature as well as skin temperature. The idea in giving a general review of our observations in this fashion is not to stress the actual temperature values discussed, but rather to point to the general harmony of the readings and to present the results in such a way that a more precise concept of what the changes involved in aortic disease may mean.

SUMMARY AND CONCLUSIONS.

1. When the human skin is soaked in water at temperatures of 45-47°C., the capillaries and venules on the one hand, and the arterioles on the other, independently dilate. These reactions are both local reactions. When higher temperatures are used, a reflex dilatation of the arterioles is observed in addition, and this spreads beyond the heated area.

2. Capillary pulsation is a physiological phenomenon, occurring in the skin or mucous membrane whenever the arterioles are sufficiently dilated, providing that the pulse pressure is normal and capillary and venule tone is not increased. A sufficient dilatation to produce pulsation is usual in the arterioles of the face of young people at room temperatures of 17-20°C.. Pulsation is brought about in the hand by immersing it in water at 45°C., providing that the arterioles are capable of dilating; it is usual in association with the vasodilatation of local inflammatory lesions, however small these may be; it occurs in the facial flush of amyl nitrite, and in other forms of bright erythema of the skin.

3. If, in the presence of normal or heightened pulse pressures, capillary pulsation in the hand is not produced by soaking the hand in water for 3 minutes at 45-47°C., the arterioles are probably incapable of dilating or are present in reduced number.

4. In aortic regurgitation, capillary pulsation is often independent of high pulse pressure, though the last increases pulsation when this is present. In patients suffering from the named valvular defect, sufficient dilatation of the arterioles is again the chief determining cause of capillary pulsation. The state of the arterioles not only chiefly determines its presence or absence, but *a fortiori* it determines its varying prominence in different skin areas.

5. The colour of the facial skin in uncomplicated aortic regurgitation is mistakenly described as pale. On the contrary, the facial skin is, if anything, more flushed and warmer than normal. In aortic disease, in which the mean blood pressure is at or below normal, the arterioles of the face can usually be shown to be wider than normal; this arteriolar dilatation is often associated with arterial dilatation: sometimes, though not usually, the

flushing of the face with arterial blood is so excessive that the patient is conscious of heat and throb in the face. The skin of the hands is affected like the face, but in lesser degree.

6. Arteriolar dilatation is opposed to cyanosis.

7. It is more accurate to associate capillary pulsation with dilated arterioles than it is to associate it exclusively with any other causative factor; and this statement is independent of the clinical diagnosis of the case.

8. It is probable that in all cases of macroscopic "capillary pulsation" the phenomenon is due to the pulse passing from the arteries into and through the capillaries, to involve in greater or lesser degree the minute skin venules. The visible pulsation is shown to be due mainly, as Boas has suggested, to pulsation of the venules, at all events in the skin of the face, trunk and upper parts of the limbs. Pulsation of the capillaries themselves contributes little in these areas; it probably contributes more in the skin of the palm and sole and in the mucous membrane of the lip.

9. There is no evidence that pulsation is conveyed from arterioles to venules through the arterio-venule anastomosis originally described by Sucquet.

10. A method of obtaining skin temperature rapidly and accurately is described, and a number of observations relevant to capillary pulsation and to the foregoing conclusions is recorded. These include observations upon the temperature of the facial skin in aortic regurgitation, in bilateral and unilateral facial erythema and in small inflammatory skin foci. The local change in skin temperature during the formation of urticarial wheals, and on closing a free anastomosis between an artery and vein, are also described and discussed.

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- ¹⁸ RICKER AND REGENDANZ. Archiv. f. pathol. Anat. u. Physiol., 1921, CCXXXI, 1-184.
- ¹⁹ SUCQUET. "D'une Circulation dérivative dans les Membres et dans la Tête chez l'Homme," Paris, 1862.
- ²⁰ SUMBAL. *Heart*, 1923, x, 271-4.
- ²¹ WEISS AND DIETER. Zentralbl. f. Herz. u. Gefasskrankh., 1920, xii, 295.



FIG. 4. (1862.) A group of terminal arterioles, capillaries and venules at the base of the finger nail in a case of aortic disease. The pulsation in these vessels is described on page 175.



FIG. 5. (1862.) A similar group of vessels in the skin on the ventral surface of the forearm in a case of aortic disease. The pulsation in these vessels is described on page 176.

THE VITAL CAPACITIES OF PATIENTS WITH CARDIAC COMPLAINTS.

By A. W. HEWLETT.

(From the Department of Medicine, Stanford Medical School.)

The vital capacity is frequently diminished when there is disease of the thoracic organs. At least two groups of causes contribute to this result. In the first place, the occupation of space which might otherwise be used for breathing obviously tends to lessen the vital capacity. Thoracic tumours, consolidations, exudates and pneumothoraces are accompanied by a reduced vital capacity. In the second place, the reduction may depend upon a restriction of the respiratory movements, whether by pulmonary fibrosis, pleural adhesions or arthritis of the costo-vertebral articulations. In tuberculosis, determinations of vital capacity have proved of value, both for estimating the amount of lung involvement and for following the progress of the disease^{3, 8}.

The vital capacity is diminished in many patients with cardiac disease^{9, 10}. This occurs particularly when the disease has affected the lungs through passive congestion and exudates into the air spaces. The mechanical effects of cardiac enlargement, of infarcts, and of pleural or pericardial exudates obviously lessen the vital capacity. In addition, passive pulmonary congestion lessens the volume of the air spaces owing to swelling of the pulmonary capillaries, and it tends to make the lungs more rigid ("Lungenstarre" of von Basch). Lundsgaard⁷ showed that patients with mitral lesions without venous congestion do not empty their lungs to a normal extent during forced expiration; and Drinker, Peabody and Blumgart⁴ found that in cats an acute passive congestion of the lungs lessened the extent of the respiratory movements.

In heart disease, vital capacity measurements have proved valuable both in estimating the gravity of the lesion, especially as regards the pulmonary congestion; and in following the progress of the disease over longer or shorter periods. The present paper is a statistical study of the vital capacity in a group of patients, most of whom complained of symptoms suggesting heart disease. Particular attention has here been paid to the association of diminished vital capacity with other objective evidences of cardiac disease.

Normal standards.—Like other biological measurements, the vital capacity varies considerably among normal individuals. Men have larger vital capacities than women. Race is of importance; for Foster and Hsieh⁵ found that the vital capacity of Chinese falls distinctly below English and American standards. In old age there is a tendency for the vital capacity to lessen. Finally body size is a factor which greatly influences the vital capacity. While all agree to this last proposition, there exists much uncertainty as to which measure of size is the most useful as a standard for estimating the normal vital capacity. The relation of vital capacity to weight, to height, to sitting height, to certain chest measurements and to various combinations of height and weight, such as that represented by the estimated surface area, have all been studied in normal individuals. None of these various measurements of size shows a very close correlation with the vital capacity. The surface area appears to be the best standard in use for estimating the vital capacity of normal individuals; yet Hewlett and Jackson⁶ found that according to this standard approximately four of every hundred male college students had a vital capacity which was less than eighty per cent. of the average normal. According to their figures, the height standard which they used was only slightly inferior to the surface area standard. Rogers¹¹, studying a group of Stanford students, found that the stem height was not materially better as a standard than the standing height. We have used a standing height standard for patients; first because it is convenient, and second because changes in weight due to obesity or anasarca do not influence this standard. For men the following formula was used:—

$$V.C. = 50 \text{ Ht.} - 4,400,$$

where the height was expressed in centimetres and the vital capacity in cubic centimetres⁶. By applying statistical methods to the vital capacity records of two hundred and sixty women students who were examined as a routine at the Stanford University Gymnasium, the following formula for college women was obtained:—

$$V.C. = 27.4 \text{ Ht.} - 1,365.$$

This formula has been used for estimating the vital capacities of our female patients. In the present paper all vital capacities have been expressed in percentages of the estimated normal, which latter was calculated from the standing height by the above formulas.

The vital capacity records discussed in the present paper were obtained from patients who had been referred to the electrocardiograph laboratory of the Stanford Medical School. Since May, 1922, it has been customary in this laboratory to measure the vital capacities of all patients sent for electrocardiograms and to express these capacities as percentages of the average normal according to the height standards just described. In the present paper five hundred records of men and four hundred records of women have been analysed. Most of these records were obtained from patients of the

TABLE I.

Vital capacities of 500 men with cardiac complaints.

Vital capacities arranged in groups.		All patients	Patients with negative chest	Enlarged hearts.	Blood pressure over 160	Left ventricular preponderance.	T inverted in lead I.	Extrasystoles.	Auricular fibrillation.	Positive Wassermann.
20 — 24	1	0	1	0	0	0	0	0	0	0.0
25 — 29	3	0	1	0	0	0	0	0	1	0.0
30 — 34	8	0	5	3	4	3	2	0	0	2.0
35 — 39	6	0	5	2	3	3	3	1	0	0.0
40 — 44	9	0	7	4	2	3	1	12	0	0.0
45 — 49	22	0	14	6	10	8	5	7	2	2.0
50 — 54	22	1	15	8	7	8	5	7	0.5*	
55 — 59	29	1	14	10	10	8	9	5	5.0	
60 — 64	35	3	22	10	12	6	6	7	5.0	
65 — 69	30	1	16	14	12	10	6	4	3.0	
70 — 74	19	3	21	15	13	8	11	5	9.0	
75 — 79	40	12	15	9	14	8	5	3	2.5*	
80 — 84	50	13	13	10	7	3	7	3	4.5*	
85 — 89	51	23	12	11	2	3	1	3	5.0	
90 — 94	46	18	10	10	5	1	7	1	6.5*	
95 — 99	39	22	4	5	2	2	4	3	1.0	
100 — 104	21	13	2	4	5	1	2	0	2.0	
105 — 109	13	9	1	2	1	1	2	1	0.0	
110 — 114	15	13	1	1	0	0	1	0	1.0	
115 — 119	6	5	0	0	1	0	0	0	0.0	
120 — 124	4	2	0	1	0	0	1	0	2.0	
125 — 129	1	1	0	0	0	0	0	0	0.0	
No. of cases...	500	140	179	125	110	76	78	53	51.0	
Average V.C. in per cent.	77.3	93.3	66.3	71.8	67.5	63.4	70.8	64.5	76.1	
Standard deviation in per cent.	20.0	13.9	17.5	18.4	17.8	16.6	19.7	17.2	19.2	

* In our statistics, as expressed in this and subsequent tables, doubtful or variable Wassermann reactions have been assigned an arbitrary value of 0.5.

medical clinic. A lesser number were obtained from patients of other clinics or from private patients whose clinical records were available for study. These patients therefore belong to a group the members of which were for some reason suspected of cardiac disease.

The data were prepared for statistical study by abstracting each history briefly on a form sheet which summarised the main findings as regards the heart. These abstract sheets were grouped according to the vital capacities recorded, averages being used when several observations were made on a single patient. Fairly satisfactory data were obtained with regard to certain clinical manifestations. With others the data were unsatisfactory or incomplete. For this reason we have not tabulated the statistical relation of

TABLE II.
Vital capacities of 400 women with cardiac complaints.

Vital capacities arranged in groups.	All patients.	Patients with negative chest.	Enlarged hearts.	Blood pressure over 160.	Left ventricular preponderance.	T inverted in lead I.	Extra-systoles.	Auricular fibrillation.	Positive Wassermann.
25 — 29	3	0	1	1	1	1	0	1	0.0
30 — 34	4	0	1	0	0	0	0	2	0.5
35 — 39	6	0	3	3	4	1	3	0	1.0
40 — 44	5	0	2	2	4	1	1	0	0.0
45 — 49	10	0	7	3	3	2	0	3	0.0
50 — 54	15	0	7	7	4	1	1	4	1.0
55 — 59	22	2	12	11	6	5	2	5	2.0
60 — 64	29	6	8	12	9	2	3	0	1.0
65 — 69	25	9	5	6	7	1	1	0	1.5
70 — 74	51	13	11	16	10	4	8	1	1.5
75 — 79	38	12	8	7	3	1	3	3	3.0
80 — 84	44	19	5	7	6	1	2	0	2.0
85 — 89	50	19	6	11	11	0	7	0	3.5
90 — 94	33	18	3	4	5	0	1	0	1.5
95 — 99	20	11	1	2	2	0	5	1	0.0
100 — 104	16	12	0	1	2	0	0	0	0.5
105 — 109	17	11	2	2	2	0	2	0	1.0
110 — 114	6	5	0	0	0	0	1	0	0.0
115 — 119	3	3	0	0	0	0	0	0	0.0
120 — 124	1	0	0	0	0	0	0	0	0.0
125 — 129	0	0	0	0	0	0	0	0	0.0
130 — 134	2	2	0	0	0	0	0	0	0.0
No of cases ...	400	142	82	95	79	20	40	20	20
Average V.C. in per cent.	77.5	87.7	65.7	68.9	70.4	58.7	76.4	56.2	74.3
Standard deviation in per cent. ...	18.4	14.7	16.7	16.3	18.4	13.7	18.9	16.7	17.7

lowered vital capacity to symptoms. Nevertheless our observations indicate that the symptoms most frequently associated with a low vital capacity were dyspnœa and cough; whereas palpitation and thoracic pain were less closely related to reductions in the vital capacity. When cough was associated with a low vital capacity, physical changes in the lungs could usually be demonstrated. In some patients these pulmonary changes appeared to be independent of the heart condition, being due to pulmonary tuberculosis, fibrosis, or pneumonia. In others the pulmonary lesions were clearly secondary to the heart disease. Dyspnœa was usually present when the vital capacity was less than 50 per cent. of the college standard; but it is noteworthy that dyspnœa of a moderate degree might also occur in patients whose vital capacity approximated the normal. Evidently therefore a low vital capacity is not a necessary factor in the production of moderate cardiac dyspnœa.

Differences between the men and women.—Separate tables were prepared for the men and for the women, and these showed certain differences dependent upon sex (see the summary in Table III). In the first place, the women with cardiac complaints less commonly showed signs of serious cardiac disease. Definite objective evidence of thoracic disease was absent in 35 per cent. of the women as compared with 25 per cent. of the men. Conversely the number of women with demonstrable cardiac enlargement, auricular fibrillation, or inverted *T* in lead *I* was distinctly less than the number of men with these changes. On the other hand, the proportion of

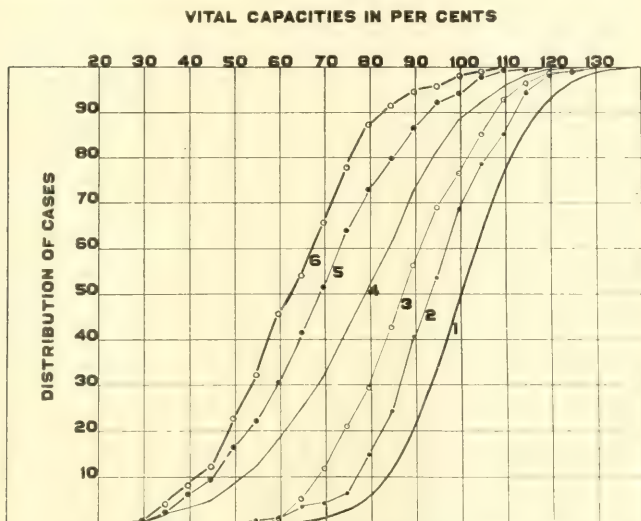


Fig. 1. Ogive curves showing the distribution of vital capacities in different groups of patients. These curves show the percentage of patients in any group who have vital capacities more or less than a given amount. 1. College standard. 2. Male patients with no objective evidence of thoracic disease. 3. Female patients with no objective evidence of thoracic disease. 4. All patients. 5. Patients with left ventricular preponderance. 6. Patients with *T* inverted in lead *I*.

patients showing a blood pressure of 160 or over and the proportion of patients with evidence of left ventricular preponderance were approximately equal for the two sexes. A second difference between the men and the women was the lower vital capacity in those women who showed no objective evidence of thoracic disease. Male patients belonging to this class showed an average vital capacity of 93.3 per cent. of the college standard, whereas

among women of this class the average vital capacity was 87.7 per cent. of the standard (Fig. 1). It appears then that our college standard was relatively high when applied to women patients. The cause of this difference between the men and the women is not altogether clear. It is possible that the difference in physique between college students and the average patient without manifest organic disease was greater for women than for men. Possibly the difference was due to the clothes worn by the patients, the women being more restricted by these than the men. However this may be, it is apparent in most of our records, that, other things being equal, the women tended to fall farther below the college standard than did the men.

Cardiac enlargement.—The vital capacities of our patients were compared with other selected manifestations of cardiac disease. Important among these was the size of the heart. Cardiac enlargement may be detected clinically either by physical or by X-ray examination. On physical examination, dependence was placed mainly upon the position of the apex beat and the area of cardiac dullness. Each may under certain conditions be subject to considerable error. The cardiac impulse, both on inspection and on palpation, may be displaced downward and to the left, not only by cardiac enlargement but by displacement of the heart and by an unusual violence of the cardiac movements (irritable heart). The area of cardiac dullness may be so obscured by distension of the overlying lung borders that it is practically useless as a measure of cardiac size. On account of these difficulties we have laid stress upon the X-ray reports in judging the heart sizes of our patients. In some instances orthodiagrams or six-foot plates were available; yet even without these, X-ray plates, taken under standard conditions, may be used to show any conspicuous enlargement of the heart. In the present series a heart has been called large whenever the X-ray report stated that there was definite enlargement and its size has been called normal whenever the X-ray report stated definitely that no enlargement was present. If the X-ray report was doubtful or if no X-ray examination had been made, then the size of the heart was judged from the physical findings, slight or doubtful physical changes being disregarded.

Using these criteria of cardiac enlargement, the vital capacities of patients showing this condition were tabulated. The average was 66.1 per cent. of the college standard. This was considerably lower than the average of our patients who showed no definite evidence of thoracic disease (90.5). It was also distinctly lower than the average for all patients (77.4 per cent.). Patients who showed a very low vital capacity with no evidence of cardiac enlargement almost invariably had definite evidence of pulmonary disease, such as advanced tuberculosis, pulmonary fibrosis, or pneumonia. Only 24 of the 261 patients with cardiac enlargement showed a vital capacity of 90 per cent. or over. It is evident from these figures that patients with enlarged hearts usually but not invariably have a vital capacity which is less than the average for patients in whom no organic thoracic disease could be demonstrated.

TABLE III.

Vital capacity summary.

MEN.					WOMEN.		BOTH SEXES.		
		Number.	Average vital capacity.		Number.	Average vital capacity.	Number.	Average vital capacity.	Relative frequency men to women.
College standard	...	1,444	100.0	260	100.0	1,704	100.0		
All patients	...	500	77.3	400	77.5	900	77.4		
Chest negative	...	140	93.3	142	87.7	282	90.5		0.8
Enlarged heart	...	179	66.3	82	65.7	261	66.1		1.7
B. P. over 160 mm.	...	125	71.8	95	68.9	220	70.8		1.1
Left ventricular preponderance	...	110	67.5	79	70.4	189	68.6		1.1
T inverted in lead I	...	76	63.4	20	58.7	96	62.4		3.0
QRS over 0.10 sec.	...	27	60.8	8	59.2	35	60.4		2.7
Auricular fibrillation	...	53	64.5	20	56.2	73	62.2		2.1
Extra-systoles	...	78	70.8	40	76.4	118	72.7		1.6
Positive Wassermann	...	51	76.1	20	74.3	71	75.6		2.0

TABLE IV.

Wassermann reactions in patients with cardiac complaints.

	Men.	Women.	Total.	Unselected clinic patients.
Wassermann, positive	45	17	62	26
Wassermann, doubtful	11	6	17	12
Wassermann, negative	346	258	604	238
Total number tested	402	281	683	276
Not tested	98	119	217	724
Total cases	500	400	900	1,000
Percentage positive among those tested	12.5	7.1	10.3	11.6
Percentage positive in total cases	10.1	5.0	7.8	3.2

Hypertension.—Patients whose systolic blood pressures averaged 160 mm. or over were classed as hypertension cases. Men and women were affected to approximately the same degree. The average vital capacity of all these patients was 70.8 per cent. of the college standard. This may be

compared with the average of 90.5 per cent. for patients with no objective signs of thoracic disease or with the average of 77.4 per cent. for all our patients. Hypertension is, therefore, in the average associated with some reduction of the vital capacity, but the reduction is less than that present in patients who showed cardiac enlargement.

Form of the ventricular complex.—The vital capacities of patients showing various alterations in the form of the ventricular complex were tabulated. Most common among these alterations were those commonly attributed to *left ventricular preponderance*, in which the main deflection of *QRS* was higher in lead *I* than in lead *II* and was inverted in lead *III*. Only conspicuous alterations of this type were included in the present tabulation. This alteration was present in 110 of the 500 male patients and in 79 of the 400 females. The relative frequency was therefore only slightly higher among the men than among the women. The average vital capacity for the entire group was 68.6 per cent. of the college standard (Fig. 1, Curve 5), which was a little lower than the average vital capacity for patients showing a blood pressure over 160 and a little higher than the average vital capacity for patients showing cardiac enlargement. Evidence of right ventricular preponderance was very uncommon in this group of patients. Only 21 showed even slight alterations of this character. Their average vital capacity was 72.3 per cent.; but on account of the small number of cases, the slight change in many of these and the wide variations in vital capacity, we do not emphasise this figure. Inversions of *T* in lead *III* were common and appeared to be of little significance. They were not tabulated. *Inversions of T in lead I*, on the other hand, were usually associated with definite reductions of the vital capacity. This change occurred in 76 of the 500 male patients and in 20 of the 400 female patients, making the relative frequency for males over three times the frequency for females. In terms of the college standard the average vital capacity for males was 63.4 per cent., for females 58.7 per cent., and for both sexes 62.1 per cent. (Fig. 1, Curve 6). These low figures emphasise again the serious significance of inversion of *T* in lead *I*. *Widening of QRS* to 0.10 of a second or more in one or more leads was observed in 27 male and 8 female patients. The average vital capacity for these patients was 60.4 per cent. of the college standard, this being the lowest average for both sexes of any tabulated abnormality. Vital capacity measurements therefore confirm the prevalent view that the most serious of common alterations in the form of the ventricular complex is a definite widening of *QRS*, the next most serious, an inversion of *T* in lead *I*, while the changes attributed to left ventricular preponderance are of lesser importance.

Cardiac irregularities.—Only two irregularities were tabulated, extra-systoles and auricular fibrillation. In tabulating *extra-systoles*, only those ectopic beats which occurred during the course of a sinus rhythm were included, the ectopic ventricular beats which were observed during auricular

fibrillation being omitted. Among our patients, extra-systoles were more common than auricular fibrillation, and their relative frequency in men was one and a half times their relative frequency in women. The average vital capacity for all patients showing extra-systoles was 72.7 per cent, which was the highest average for any of the groups of cardiac abnormalities tabulated. *Auricular fibrillation* was about twice as frequent in men as in women. The average vital capacity for all patients was 62.2 per cent, of the college standard. This was one of the lowest of the tabulated groups, being approximately the same as the average for those showing inversion of *T* in lead *I* and only slightly higher than the average for those with widened *QRS*. The low vital capacity in most patients showing this irregularity needs emphasis because there is at times a tendency to minimise the gravity of this arrhythmia^{2, 12}. Of 53 men with auricular fibrillation only five showed a vital capacity exceeding 90 per cent, of the college standard, while of 20 women only one showed a vital capacity above 80 per cent., and the vital capacity in this case was taken during a paroxysm of fibrillation. If the vital capacity could be regarded as a rough measure of cardiac efficiency it would appear that patients with auricular fibrillation only exceptionally show a normal efficiency. The effect of changes of rhythm, either spontaneous or induced by quinidin, upon the vital capacity was followed in a few of our patients. Briefly it was found in these few patients that no great change in the vital capacity occurred immediately after a change in rhythm but that when the restored sinus rhythm had persisted for some days or weeks there was in most instances an improvement of the vital capacity. This beneficial effect of a change to the normal rhythm has been noted by Burwell and Dieuaide¹ and by others.

The Wassermann reaction.—A summary of the Wassermann reactions in this group of patients is shown in Table IV. Positive reactions were almost twice as common in the men as in the women. Of the total 900 patients 683 were tested and of these 62 showed positive reactions and 17 showed doubtful or variable reactions. In order to ascertain if positive Wasserman reactions were relatively more common in patients suspected of cardiac disease the records of 1,000 consecutive patients admitted to the Stanford out-patient clinics during portions of September and October, 1922, were examined, and it was found that of 276 patients tested 26 showed positive and 12 doubtful or variable reactions. Owing to the different proportion of patients tested, the two sets of figures are hardly comparable. Positive reactions among those tested were slightly less common in the cardiac group; but positive reactions were considerably more common in this group if we consider the total number of patients (see Table IV). It seems likely that if an equally high proportion had been tested among all those who came to the out-patient clinic the percentage of positive tests would have fallen below the percentage for the cardiac group. However this may be, it is evident from Table V that a positive Wassermann reaction was not accompanied by

TABLE V.

Wassermann reactions and their vital capacity.

	Number of cases.	Average vital capacity.	Standard deviation.
All men	500	77.3	20.6
Men with positive Wassermann	51	76.1	19.2
All women	400	77.5	18.4
Women with positive Wassermann	20	74.3	17.7
All patients	900	77.4	19.3
All patients with positive Wassermann...	71	75.6	18.8
All patients except those with evident luetic aortitis	884½	77.6	19.3
Patients with positive Wassermann but without evident luetic aortitis	55½	78.3	18.4

VITAL CAPACITIES IN PER CENTS

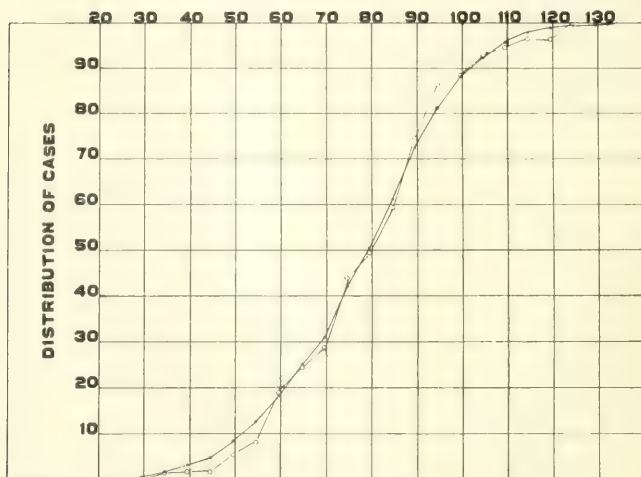


Fig. 2. Ogive curves showing the distribution of vital capacities in our patients after omitting those who showed objective evidence of syphilitic aortic insufficiency or aneurism. The smoother curve with dots is for all patients. The less regular curve with circles is for patients with positive Wassermann reactions.

any striking reduction in the average vital capacity of our patients. The average vital capacity for patients showing a positive reaction was 75.6 per cent., while the average for all patients was 77.4 per cent.. This slight reduction is the more remarkable when we consider that syphilis is an important cause of serious aortic disease. In its earlier stages, however, luetic disease of the aorta does not cause the pulmonary congestion that appears to be mainly responsible for the reduced vital capacity of cardiac patients. Hence a depressing effect of such lesions upon the vital capacity would be evident only in their later stages. If all cases with a positive Wassermann reaction and with definite signs of aortic insufficiency or aortic aneurism were omitted from consideration, then the average vital capacity among patients with a positive Wassermann reaction was 78.3 per cent., while the average for all cardiac patients after making the same omission was 77.6 per cent. (Fig. 2). In other words after omitting the easily diagnosed cases of syphilitic aortitis, the presence of a positive Wassermann reaction exercised no unfavourable effect upon the vital capacity. From this we conclude that so far as the present series of cases is concerned, syphilis was a negligible factor in the production of serious cardiac failure except when evident lesions of the aorta were present.

Discussion. In heart disease vital capacity measurements are of interest because they furnish a rough measure of that type of insufficiency which depends upon congestive changes in the lungs. This measure is at best only an approximate one. First, because causes other than cardiac disease may reduce vital capacity, and second, because by any standard of measurement now in use the vital capacities of normal individuals show wide variations. Even a homogeneous group, such as apparently healthy college students, contains occasional individuals whose vital capacity is seventy-five per cent. or less of the average normal.

When we pass from college students to the general population it is but natural to expect—first, that still wider variations from the average will occur, because the group is less homogeneous, and second, that the average vital capacity will be lower because the average physique of college students is better than that of the general population. Hutchinson's male subjects showed an average vital capacity of only 86.3 per cent. of our college students, after making allowance for the difference in height. This marked reduction was due in part to the fact that he examined men of all ages and from all walks of life: in part, it may be attributed to some undetermined difference in his technique or to a general improvement in the English physique during the past seventy years. Our patients with cardiac complaints but with no objective evidence of thoracic disease showed a wider variation in their vital capacity than did college students. The standard deviation for this group of patients was 14.7 per cent. while for college students it was approximately 13.0 per cent.. Furthermore, the average vital capacity for this group of patients was 90.5 per cent. of the college standard, the difference

being greater for the women than for the men. Roughly speaking a vital capacity reading is low when it falls below 75 per cent., but it can be regarded as definitely abnormal only when it falls below about 60 per cent. of the college standard. This statement does not apply to averages, for in them individual fluctuations have been eliminated. An average difference of only a few per cent. may well be significant. Nor does it apply to a series of observations on a given individual. Here changes of 5 per cent. or more are significant.

Returning to a consideration of the averages discussed in the present paper one may say that these express the tendency of certain cardiac abnormalities to be accompanied by the pulmonary changes which reduce vital capacity. In other words, our averages express the seriousness of various pathological changes from the standpoint of a congestive type of cardiac insufficiency. Viewed from this angle it is seen that hypertension and particularly extra-systoles are frequently not accompanied by cardiac insufficiency; that auricular fibrillation, negative *T* in lead *I* and widening of *QRS* are usually accompanied by insufficiency, and that an enlarged heart and definite electrocardiographic evidence of left ventricular preponderance occupy an intermediate position. Such a rating of the above abnormalities agrees in the main with prevalent views as to their significance; but vital capacity averages give to the rating a more definite numerical value.

CONCLUSIONS.

(1) The vital capacity of college students based on a height standard was considerably higher than was the vital capacity of patients with cardiac complaints and without objective evidence of thoracic disease. According to the standards that we have used this difference was greater for women than for men.

(2) Vital capacity readings between 60 and 75 per cent. of the college standard are suspiciously low; those less than 60 per cent. are almost uniformly abnormal.

(3) In our series of patients with cardiac complaints, serious lesions were more common among the men than among the women.

(4) The symptoms most commonly associated with low vital capacity were cough and dyspnoea.

(5) The seriousness of the various tabulated manifestations of heart disease as judged by vital capacity averages was, in descending order:—extra-systoles, hypertension, left ventricular preponderance as expressed

electrocardiographically, enlarged heart, *T* negative in lead *I*, auricular fibrillation, and, lastly, a widened *QRS* group.

(6) If cases of evident aortic insufficiency and of aortic aneurism were omitted, a positive Wassermann reaction in our patients was not associated with any reduction of vital capacity. We infer that syphilis is in the average a small factor in the production of serious cardiac failure except when it involves the aorta or the aortic valves.

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VASCULAR REACTIONS OF THE SKIN TO INJURY.

PART II. THE LIBERATION OF A HISTAMINE-LIKE SUBSTANCE IN INJURED SKIN : THE UNDERLYING CAUSE OF FACTITIOUS URTICARIA AND OF WHEELS PRODUCED BY BURNING ; AND OBSERVATIONS UPON THE NERVOUS CONTROL OF CERTAIN SKIN REACTIONS.*

By THOMAS LEWIS and RONALD T. GRANT.

(*Cardiac Department, University College Hospital Medical School.*)

PRELIMINARY REMARKS.

IN a previous article¹⁹ one of us has reported upon the vascular changes which occur on stroking the skin in patients suffering from the condition commonly described as "factitious urticaria" or "dermatographia." It has been pointed out that those changes, which result in whealing of the skin, are not peculiar to the urticarial skin, the reactions are identical with those called forth in normal skins when these are subjected to stronger or repeated stimuli of the same kind. Factitious urticaria constitutes in exaggerated form a physiological response of the skin. That being the case, the skin, in which whealing and its correlated changes are elicited by a single stroke, enables us to investigate conveniently and in completer fashion the normal reactions to more vigorous or numerous stimuli of the same order. In studying factitious urticaria we are studying reactions which belong fundamentally to the normal mechanism, or mechanisms, of inflammation and repair.

The present studies start from this standpoint and embody a fuller investigation of the stroke reactions, taking advantage of the peculiar susceptibility of certain skins to this form of damage. It was also a chief object closely to compare the skin's response to the stroke on the one hand and to a chemical stimulus on the other, it being already known that a chemical stimulus may call forth reactions resembling superficially at least those resulting from mechanical injury. For the last purpose, and at the suggestion of our colleague, Dr. H. H. Dale, we chose histamine. Our

* Observations undertaken on behalf of the Medical Research Council.

report will largely focus itself upon the similarities between the skin's reaction to stroking and to the introduction of histamine, and upon the meaning of these similarities.

To permit of wider generalisation we have ultimately extended our observations to other forms of damage, more particularly to the response to scalding heat, and also to a lesser extent to punctures and scratches. All these stimuli, as will be seen, eventually call the same mechanisms into play.

Cases of urticaria factitia. Most of the observations recorded in this paper have been carried out upon three cases (*Subjects 1, 2 and 3**) of chronic factitious urticaria. Many of the reactions have also been witnessed in two other cases (*Subjects 4 and 5*), though these two have been less extensively investigated. Many of them have been seen in normal skin stroked, not once, but repeatedly. The five urticarial cases have all been of the same type. Wheals have followed after single firm strokes of the skin in a few minutes. In none of these patients was there any suggestion of spontaneous erythema, spontaneous urticaria, eczema or asthma, conditions not uncommonly associated with factitious urticaria. The patients came under observation primarily either for the skin condition (*Subject 2*) or more frequently for various maladies unconnected with it, the urticaria being detected during a routine examination. Our sixth case has been used for one observation only, namely, for collecting wheal fluid to puncture into a normal skin. This case is that of a young woman in good health, who notices occasional patches of erythema with small central wheals on the face and arms, and who blisters easily in strong sunlight. The stroke wheals were first discovered when we searched for them in her.

Method of producing histamine wheals. Whealing of the skin by histamine was first described by Eppinger¹⁷. It is effected by scarifying the skin and subsequently applying a dilute solution of this tissue poison. Histamine wheals were subsequently further explored by Sollmann and Pilcher²⁰, who not only used scarification but introduced the ingenious mucuna method. In this they rub the sharp hairs of mucuna into the skin and apply histamine, which enters through the perforations. We have tried a method similar to that of the last workers, substituting spun glass for the hairs. Groups of wheals may be obtained by this method, as with mucuna or scarification; but both are really unsuitable for precise and repeated observations. Scarification and friction with sharply pointed material is not sufficiently controllable and itself yields a considerable skin reaction; moreover, there is little or no guarantee that a constant dose is introduced or that the same number of tissue points are affected at a single application. We have tried and abandoned several other methods. Thus, measured doses of histamine can be forced into the skin through glass tubing drawn to a capillary point;

* The subject numbers correspond with those of Part I.

but in practice we find the poison to be distributed too irregularly in the skin. Another method is based upon the stinging hairs of nettles: a glass tube is drawn and redrawn into an extremely fine capillary point, and the whole filled with the solution. This point easily and almost painlessly pierces the skin and carries in its own dose of histamine. The method gives sufficiently constant results providing that one such pointed tube is used. If several or many tubes are to be used, and this becomes necessary in using different solutions, in replacing breakages and in discarding tubes which become blocked, it is hardly possible to draw these tubes so that they have equal sharpness and leave behind equal doses on withdrawal. In practice we have found the most suitable method to be a more simple one: a small drop of the solution is placed on the skin and the skin is pricked through the centre of this drop with a fine needle. The drop of histamine is then removed by lightly dabbing it with a handkerchief, though its removal does not appreciably affect the result. A device for regulating the pressure exerted on the needle was found to have no material advantage: it is sufficient to hold the needle between the finger and thumb and to exert the pressure which practice shows to be effective. In this way wheals of very constant size are produced, but to safeguard our observations against error arising from an occasional underdose of histamine, it has been our habit to put down three such punctures in a row at intervals of about $1\frac{1}{2}$ cm.* For puncturing into the human skin two solutions mainly have been employed, namely, 1 in 3,000 and 1 in 30,000 of the base, the salt being dissolved in normal saline.

In the following account of histamine and stroke reactions we do not always give protocols. Were this to be undertaken systematically, this paper would reach an inordinate length. It may be taken for granted that no observation is described which has not been repeated a sufficient number of times: that none is described which has not been repeated upon at least two, and usually upon three or more individuals. Protocols and tabulated statements are used where it is necessary to emphasise, to refer to illustrative series of measurements, or where our observations have lacked complete uniformity and it is desired to draw attention to the fact.

INITIAL COMPARISONS OF HISTAMINE AND STROKE REACTIONS.

The broad features of the reaction to histamine puncture and stroking. The reactions of the skin in urticarial patients in response to stroking have been described fully in a previous paper. They consist essentially of (a) a central and sharply defined red line restricted to the line of stroke and due to a local dilatation of the superficial capillaries, venules and terminal arterioles, (b) a bright red flush having irregular margins, and caused by

*The histamine employed in our work was given to us by Dr. H. H. Dale from his own stock and is that used by him in his published experimental work. It is the synthetic and crystalline di-phosphate of β minazolyethylamine obtained from Messrs. Burroughs and Wellcome, who supply the substance under the trade name of Ergamine acid phosphate.

dilatation of the arterioles, over the surrounding area of skin, and (c) the appearance of a raised wheal over the line of stroke. Precisely similar reactions occur after puncturing the skin with histamine. The red spot (as opposed to the red line on stroking) is best displayed on an arm in which the vessels have been occluded abruptly, after the venous pressure has been raised a little. It is then circular, has a diameter of about 3 millimetres, is purple in colour, and its edges are usually sharply defined. On an arm in which the circulation is intact, it is never so distinct, since it is masked by the accompanying arteriolar flush. The surrounding flush is distinct or vivid on an arm the circulation of which is intact, but is prevented, as is the surrounding flush of the stroke reaction, when the vessels to the limb are occluded. The histamine flush is best displayed by puncturing an arm rendered cyanotic by congestion; the flush then stands out as a bright red patch on a blue background, showing it to be due to an arteriolar dilatation. It has a diameter of 2, 3, or more centimetres, an irregular margin and often includes small outlying and detached areas. Slight capillary pulsation in the flushed area is frequently to be detected as it is in the flushed area following a stroke. The histamine wheal is hemispherical and appears over the area covered by the red spot: it has a usual diameter of about 3 millimetres. Though they cannot be determined precisely, the times of the histamine and stroke reaction are very similar, a fact abundantly illustrated to us in stroke and histamine reactions carried out simultaneously on the same arms under a variety of conditions. To illustrate, in an urticarial subject the arm was firmly stroked and at the same instant a histamine puncture (1 in 3,000) was put down.

- After 20 secs. . . red line begins.
- After 30 secs. . . flush begins in both areas.
- After 1 min. 10 secs. stroke wheal begins.
- After 1 min. 20 secs. histamine wheal begins.
- After 3 mins. . . both wheals almost full and pink.
- After 8 mins. . . both wheals full and pale.
- After 47 mins. . . both wheals pale and diminished.

Using the thermoelectric couple, described in a previous communication²⁰, observations have been made upon the change in the skin temperature in response to histamine punctures and stroking; those which chiefly concern us were undertaken upon the skins of urticarial subjects. In such a subject the back is stripped and exposed to the air of the room at 20° C. for some while, so that its temperature may become constant. The back is now searched with the testing junction to find two symmetrical areas of skin which have the same temperature: a third area is chosen as a control. When these three skin areas are found to be giving constant temperature readings, the junction being moved from one to the other in order and at suitable

time intervals, one of the symmetrical areas is punctured through 3 closely set drops of 1 in 3,000 histamine, while the other is firmly stroked. Temperature readings are continued at regular intervals from the three areas and are subsequently charted (Fig. 1). In the illustration given (from one of three patients) the average temperature of the histamine and stroke areas was each approximately 33°C .; in each instance the rise of temperature began about 1 minute after the flush was first seen and continued for about $1\frac{1}{2}$ minutes, when it reached its height, the curve then continuing as a plateau. Meanwhile the temperature of the control area (C) remained unaltered. In this instance, the temperature was maintained at its maximum longer in the case of histamine than in the case of the stroke reaction, the first temperature being maintained to the end of the observation, the last beginning to fall at about the 11th minute of the chart, and subsequently continuing at a lower level than that of the stroke wheal.* The full temperature of each

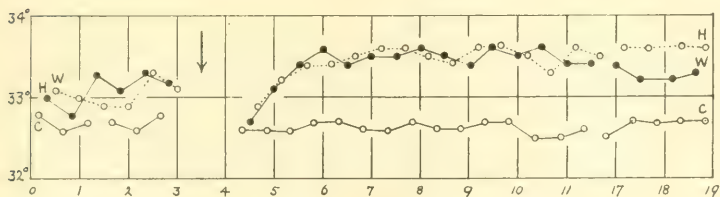


Fig. 1. *Subject 2.* A chart of skin temperature. H, skin area punctured with histamine (1 in 3,000); W, skin area whealed by a firm stroke; C, control area. The stimuli were applied at the point marked by the arrow. The readings were taken from the skin immediately adjoining the wheal. Time in minutes.

was maintained for many minutes after the flush had begun to subside and after the wheals themselves had begun to pale.† The temperature curve, when compared with the varying brightness of the flush, is found to be delayed at all phases: that is but natural since some little time is required (about 1-2 minutes) for a skin to be warmed to its new point when it receives more blood, and some time is taken for it to cool when the additional blood supply is withdrawn. The delay in temperature fall is too great to be accounted for in this fashion, however. The chief point which we desire to emphasise is the similarity between the two temperature curves: in the present instance that is the case both so far as time relations and amplitudes are concerned.

* This did not occur in the other two patients.

† A relation witnessed in all three patients.

The amplitude of the stroke curve is variable from subject to subject : in the present instance the temperature rise is a little more than $0.5^{\circ}\text{C}.$ The particular curves were taken from a patient in whom the reactions were relatively slight. In another patient the temperature rise amounted to 2 or $2.5^{\circ}\text{C}.$, the flush and subsequent whealing being very conspicuous : in this case the histamine reaction fell a little short of the stroke reaction, but the curves presented similar forms and time relations.

To sum up, the reactions of urticarial skins in response to histamine and in response to stroking, so far as they have as yet been examined, appear to be identical : they are similar in all their details. The extent of the reaction and its time relations, in the case of histamine, is naturally dependent in some measure upon the dose of the poison introduced into the skin : when a 1 in 3,000 solution is used, the time relations of the reaction and that of the response to firm stroking are also very similar.

Starting from these simple observations, and being impressed by the similarities of the two reactions, we have proceeded to examine them side by side more critically.

Variation in the size of wheals over different regions of the body. As is well known, wheals are produced by stroking, in the susceptible, more readily on the skin of the trunk than upon that of the limbs. Variation is particularly well displayed on the forearm. If a single firm stroke is run from the elbow to the wrist, the wheal which follows is conspicuous at the elbow and almost or quite invisible at the wrist. The wheal when fully developed shows a gradual decrease in height on passing down the upper part of the forearm and, about the junction of the middle and lower third of the arm, there is usually a sharper decrease in size, sometimes almost to invisibility. If a row of histamine punctures is put down parallel to the stroke and the wheals are subsequently compared, it is found that the dimensions of histamine and stroke wheals decrease *pari passu* with great regularity. Both stroke and histamine wheals are fuller on the shoulder than upon any part of the forearm. The similar variation in the two types of wheal is probably due in large part if not wholly to varying thicknesses of the true skin. The skin at the wrist is known to be materially thinner than that of the forearm itself. The similar variation in the wheal produced by histamine and stroke has in this instance no particular significance. In using the forearm to test wheals developing in different circumstances, it is necessary that the wheal and its control should be laid down side by side.

Effects of venous congestion and of impeding the circulation. If the venous pressure in the arm of an urticarial subject is raised to 70 mm. Hg. or more, the wheals subsequently produced by stroking the arm are reduced in size, the reduction becoming greater as the pressure is raised (see Part 1), the same statement applies to histamine wheals. The following is a sufficient illustration of repeated observations.

An armlet was placed on the left upper arm of a normal subject whose blood pressures were 127 (systolic) and 88 (diastolic) and raised to 50 mm. Hg. pressure. At the end of 1 minute both arms were punctured with 1 in 30,000 histamine. At the end of 3 minutes a full wheal was present on the right arm, and a smaller one on the left. The two wheals were about equal two minutes later. The observation was repeated, using a pressure of 70 mm. Hg. : 4 minutes after puncturing with histamine a small wheal appeared on the congested arm. When developed it was much smaller than that on the control arm. Repeated at 90 mm. Hg. no wheal had developed

5 minutes after the puncture. These observations were now repeated, using the 1 in 3,000 histamine, and similar results were obtained.

Thus an increase of venous pressure reduces the rate at which histamine wheals develop and under high venous pressure (70-90 mm. Hg.) the wheals when allowed to develop fully are reduced or much reduced in size. As the venous pressure approaches systolic pressure the reduction becomes even more conspicuous. We see that the effect upon the histamine and stroke wheals of venous congestion is similar. In the case of the stroke reaction it has been argued (Part I) from this and similar observations, in which suction is applied to a developing wheal, that the output of fluid is not controlled appreciably by the differential pressure existing between blood content and tissue spaces, and that distension of the small vessels is not the determining cause of increased permeability. The slow development of the wheal is due to inadequate blood flow through the skin. The argument is equally applicable to histamine wheals. A large and rapid output is only possible in the presence of a greatly increased blood flow, a statement which applies to both forms of wheal.

If the circulation to the arm is occluded, no stroke wheal is observed on the affected skin, although it is watched for long periods of time (up to 25 minutes); the same statement applies to the histamine wheal. The fluid constituting the wheal is in each case derived directly from the blood vessels.

Pressure required to prevent wheals developing. In Part I it has been shown that a considerable pressure (from 30 to 50 mm. Hg.) is required to prevent a stroke wheal from appearing. The same is true of histamine wheals, though the pressure required varies to some extent according to the strength of histamine employed. If a 1 in 3,000 solution is used, the critical pressure which is just sufficient to prevent the wheal developing is much the same for both stroke and histamine wheal. The following is an illustration of tests on two patients.

Simultaneously a firm stroke and three histamine punctures (1 in 30,000) were laid down on the upper arm of an urticarial subject. A sphygmomanometer armlet was at once applied over the punctures and the pressure in it raised to 40 mm. Hg. and held there for 4 minutes. On rapidly removing the cuff a slight stroke wheal was found, but no histamine wheal. Both had developed fully three minutes after the release. The strength of the histamine was now changed to 1 in 3,000 and the procedure repeated in exactly the same way at pressures of 50, 45, 35 and 30 mm. Hg.. At the 50 pressure no wheals had developed at the time of release (4 minutes); at 45 mm. pressure traces of stroke and histamine wheals were found at the release; at 35 pressure definite though reduced wheals were found. The reductions were very similar in degree in the two series.

Thus the pressure required to prevent the 1 in 3,000 histamine wheal and a stroke wheal developing is much the same. This observation, in the

case of stroke wheals, has been used to show that an essential factor in their production is an increased permeability of the vessel wall as opposed to exaggerated filtration pressure; and that the increased permeability is independent of distension of the small vessels. Similar arguments may be applied to the histamine wheal.

Effect of cooling the skin. If before or immediately after stroking the skin of an urticarial subject, the skin is cooled by immersion in water to 12°C., the rate at which the wheal develops is much retarded as compared with a wheal developing on skin at normal temperature. Thus at the end of 4 or 5 minutes only a diminutive wheal is seen. If the arm is withdrawn from the cold water at this time, the wheal continues to develop and in instances where it is warmed by re-immersion in water at 36°C. it comes to its full size in about 15 minutes. The effects of cooling upon histamine wheals (1 in 3,000 or 1 in 30,000) are identical, whether these are produced on the skin of normal or urticarial subjects. In the last we have put down strokes and parallel lines of histamine punctures, immersing the lower halves of these lines in cold water and leaving the upper halves exposed to the atmosphere. In these observations we have found the stroke wheals and wheals produced by 1 in 30,000 histamine to be diminished in much the same degree at the end of 5 minutes; after this interval the size of the 1 in 3,000 histamine wheals is very definitely less than normal, though the reduction is somewhat less in its degree than is that of stroke wheals.

Delay in development upon a cooled skin is sufficiently explained by the decreased blood flow to the skin, an interpretation which may be applied equally well to the two varieties of wheals.

Effects of heating the skin. The forearm of an urticarial subject is immersed in water as hot as can be borne comfortably (45° to 47°C.) for 3 minutes to a line drawn on the skin. The arm is withdrawn and a firm stroke made which passes over the line dividing immersed from unimmersed skin; the arm is then re-immersed to the original line. Within five or six minutes after the stroke a full wheal has developed over the unheated skin, but over the heated skin it is either of much reduced size or it is absent; these reduced wheals fail further to develop if the length of heating has been sufficient. This observation has given consistent results in a number of patients. The same result is obtained with dry heat. Thus the back of a patient was exposed to the heat of an electric lamp and an area a few centimetres in diameter well reddened. The skin was then stroked firmly right across the heated area. A conspicuous wheal appeared both above and below the heated area, but none could be detected over the heated skin itself. When it is desired to control the reaction upon a symmetrical area of skin, one arm is heated and the other left exposed to room temperature. The results are the same, the heated skin yielding a wheal less or much less prominent than that appearing on the control arm.

Similar results are obtained with histamine wheals on normal and urticarial skins (1 in 3,000). The procedure is similar, except that instead of stroking the skin a line of 4 punctures is put down; two of these are immersed in hot water and two remain on the unimmersed skin exposed to room temperature. The reduction of histamine wheals by heat, though conspicuous, is somewhat less so than is the reduction of stroke wheals.

The results described are those which follow when the stimulus is applied to an arm in which heat has produced already a full vascular dilatation. If the stimulus is put down first and the arm is subsequently heated, the effect is variable according to the time interval which elapses between the two procedures. A line is drawn around the middle of the upper arm of an urticarial subject to mark the level to which it will be immersed, and a series of firm strokes is put down in the length of the limb. The strokes are laid down so that half of each lies above and half below the immersion line; they are laid down at $\frac{1}{2}$ -minute intervals (or less) for a period of 2 minutes, when the arm is immersed in water at 44-45°C.. The wheal begins to show above the water line in about 1 to 1½ minutes and gradually develops to the full. If the arm is now withdrawn it is found that lines laid down 1 to 1½ minutes before the immersion began, have developed equally or almost equally throughout their length. On the other hand, those which were laid down later are reduced in size or fail to appear below the water line, the change in prominence being sharp at the water line. Broadly speaking, if the heat is not applied until about the time when the wheals begin to show themselves, its application seems to have only an inappreciable effect on the subsequent size of these wheals.

The probable meaning of these phenomena will be discussed more conveniently at a later stage. Meanwhile, it is sufficient to note that similar statements hold good if lines of histamine punctures are substituted for the strokes.

Comment.

The foregoing observations are relatively simple comparisons between stroke and histamine wheals; certain of them are introduced at this stage to simplify the description of more complex observations which are to follow. It is suitable here to review the most essential resemblances so far elicited.

The reactions to stroke and histamine present similar time relations, and it has been shown that the reaction in each case consists of:—

(a) A local dilatation of the minute skin vessels which, since it occurs when the circulation is at a standstill, is a primary dilatation of these vessels. It is not dependent upon simultaneous dilatation of the arterioles.

(b) A surrounding flush, which is due to widespread dilatation of the skin arterioles; that is known because the flush is of a bright arterial colour;

because it fails to appear if the circulation is occluded ; because in its area it abolishes cyanosis produced by congesting the veins of the arm ; and because it frequently presents capillary pulsation.

(c) An output of fluid into the tissues to constitute a wheal. This fluid comes from the vessels and the rate at which it is thrown out is largely controlled by the rate of blood flow through the tissue. A greatly increased blood flow is essential to rapid whealing ; any interference which impedes the blood flow checks the rate of fluid output. The fluid can be thrown out against relatively high external pressures, showing that whealing is not simply dependent on increased filtration pressure, and evidencing an increased permeability of the vessel wall. The last is not due essentially to simple distension of the vessels, but to some independent change in the vessel wall.

It is clear from these preliminary observations that we have to deal with a complex reaction ; it is a threefold reaction, each constituent part of which is independent of the other parts. That the local dilatation of venules and capillaries is independent of arteriolar dilatation has been demonstrated ; that increased permeability is independent of the vasodilatation as a whole has also been evidenced and will receive further and stronger support at a later stage, when it will be seen that increased permeability may fail in the presence of a full vascular reaction. That the arteriolar dilatation stands by itself is proved by the observations on the influence of nerve supply which shortly follow.

Reaction to burning.

In later sections of this article, the local reactions to excessive heat are dealt with from time to time : these reactions are spoken of as burn reactions. The stimulus has been applied by a method previously described. The end of a thin test tube filled with boiling water is brought momentarily against a small area of skin ; the time it is applied is regulated by the subject, who withdraws his arm as soon as the heat begins to be intolerable. To obtain a good vascular reaction the tube is re-applied to the spot about 6 times. When two areas are to be stimulated equally, they must be heated for precisely the same periods, with tubes of equal thickness and containing water at the same temperature. This simultaneous heating is particularly important when one area so heated is anæsthetic.

The reactions to excessive heat so applied have been in part previously described²⁰. They consist of a local reddening of the skin, which soon becomes surrounded by a widely spreading and bright arterial flush, the margin of which is irregular, and which often presents outlying patches. If the stimulus is repeated a greater number of times, a low flat wheal appears over the area to which the heat has been applied ; if repeated further the skin rises and a blister is produced. Heat wheals can be produced by repeating a stimulus which is not intolerable if this method is followed.

Influence of nerve supply to the skin.

It is stated by Ebbecke¹⁶ that stroke wheals will develop upon anæsthetic skin: he instances a case of factitious urticaria in which a local patch of anæsthesia followed a wound, and states that the wheal developing on this area differed from that on the sensitive skin chiefly in lacking a widespread surrounding flush. According to Ebbecke anæsthesia of the skin has no influence upon the red line produced by stroking but abolishes the flush. It is probable that the nerve lesions with which this author was dealing in describing the effects on the flush were old-standing lesions, though this cannot be ascertained in his text.

In earlier observations, Müller²¹ records an instance of anæsthetic skin, due to a peripheral nerve lesion, and finds that the red flush which normally soon surrounds a pin prick or scratch does not appear on such skin. Again we are left in doubt as to whether the nerve lesion was new or old. In the same article Müller instances cases of paraplegia, following caries of the spine or fractures of the spine and states that while the flush in response to scratching is preserved in skin corresponding to segments of the cord below the area damaged, it is abolished over a narrow zone corresponding to the actual level of the lesion. He cites two cases to this effect, and the peripheral nerve lesion, in support of his conclusion that the flush is a reflex depending upon the integrity of the spinal reflex arc. These observations of Müller appear to have influenced later writers^{16 & 18}, who seem to accept his conclusion. There are, however, certain reasons for doubting its validity. When the skin is pricked, a patch of skin precisely surrounding the point pricked becomes flushed, an area perhaps no more, perhaps less, than a square centimetre in extent: when a long scratch is put down on the skin, the line of scratch and a narrow band on each side of it is precisely involved, irrespective of the part of the body scratched, and without the reaction indicating on the skin the junctions between the several spinal cord segments which would necessarily be involved in such a reflex as is suggested. If the phenomenon is a spinal cord reflex, then every square centimetre of skin would require to be represented in the corresponding segment of the cord before even approximately accurate reflexion of the stimulus could occur. The Lovén reflex²¹, in which vasodilatation of the skin of the ear as a whole can be produced by stimulating the central end of the sensory nerves supplying this region, is a coarse affair by comparison and may well be a distinct phenomenon. Now Bruce⁹ has shown that when mustard oil is applied to the conjunctiva, the vasodilatation which occurs is independent of the central nervous system, since it is seen when the sensory nerves to the conjunctiva are freshly cut: it is abolished when these nerves are allowed to degenerate and is reduced when their endings are anæsthetised locally. These experiments led him to the view that in the conjunctiva the reaction is an axon reflex; it is easy enough to understand how a local reflex of the kind Bruce described can limit the field of vasodilatation precisely to the

immediate neighbourhood of the injury. It would surely be extraordinary finally to conclude that the reflex in the case of the conjunctiva is purely local, while a similar and precise reaction on the skin of the body is called forth through the spinal cord. We were the more discontented with the evidence since Breslauer⁸ has shown clearly that the erythema, which follows an application of mustard oil to the skin, is also a local reflex. This occurs equally well when the sensory nerve stems to the part are intact or freshly divided (by section or anæsthesia), but is abolished when these nerves degenerate or are paralysed by local injections of novocaine. Müller's cases of spinal cord damage, as these are described, form insufficient evidence that the flush which surrounds an area of mechanically stimulated skin depends on the integrity of the spinal reflex arc; no evidence is presented to show that the sensory nerves were undamaged and undegenerate, presuming, what is probable, that his cases were instances of long standing damage, degeneration of the sensory nerve is not to be excluded in the absence of evidence to this effect. In view of what has been said, we have considered it desirable to reinvestigate the matter and to obtain reactions with a variety of stimuli.

Local skin anæsthesia. Using a solution of 2 per cent. novocaine, skin areas of the forearm 2-4 centimetres in diameter have been anæsthetised by subdermal injection. If the injection is made just beneath the true skin,* the area takes a bright red colour and becomes entirely insensitive to touch, pain and heat.† This reddening of the skin interferes with subsequent observations upon the vascular reactions. To investigate the flush which normally surrounds a histamine wheal or a burn of the skin, it is necessary that the area anæsthetised should be small or that the stimulus be put down near the edge of the anæsthetic area; accurately to determine the extent of the flush, the veins of the arm are congested previously to 40 or 50 mm. Hg. pressure. The flush then shows red on a blue background. If a group of histamine punctures is laid down on an anæsthetic area and a control group is put down on normal skin, it is easy to demonstrate that both the histamine flush and the burn flush is abolished, since in the control areas they spread widely, while the edge of the anæsthetic flush is not extended although the stimulus is put down quite near to its margin. This observation has been made decisively with histamine on three separate subjects on more than one occasion and is illustrated by Fig. 2. The effect upon the arterial flush surrounding a local burn is similar; the flush is abolished, as we have been able to demonstrate repeatedly. If the anæsthetic is injected a little deeper beneath the skin, the redness of the skin is less conspicuous and may amount to a faint red flush only. In such instances the flush surrounding

* Injections actually into the true skin are of less value since a wheal is formed by the injected fluid, and the area becomes white owing to collapse of the skin vessels. Its effects on the flush surrounding histamine punctures are the same as those described for deeper injection.

† To avoid repetition we shall in future employ the term *anæsthesia* to imply the complete loss of these three sensations.

histamine punctures or burns would be detected on the anæsthetic area were it to occur; it does not do so, though we regard these results as less important since the paralysis of the nerve endings is more questionable. When histamine is put down on skin so anæsthetised wheals usually develop, but they are of reduced size as compared to the control wheals; they are reduced the more conspicuously the more the skin is flushed, and in the case of injections which have flowed immediately beneath the true skin, often fail to appear. The reduced size of the histamine wheals is probably connected with the increased vascular supply to the skin. A number of observations with the thermopile has shown a conspicuous rise of temperature ($2\text{--}3^{\circ}\text{C.}$) in the skin so anæsthetised (for instance from $31\cdot5^{\circ}$ to $33\cdot4^{\circ}\text{C.}$).

Histamine wheals also fail to develop fully when put down on skin artificially heated or on skin showing a bright flush from other causes, for example on the flushed skin surrounding an urticarial wheal.

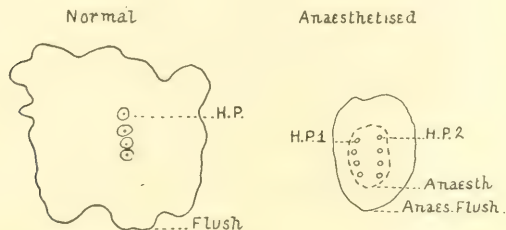


Fig. 2. Normal subject (· 2 3). To the left is shown the area of flush surrounding 4 histamine punctures (1 in 3,000); laid down on normal skin. To the right is shown an area of complete anæsthesia, produced by subcutaneous injection. The area of the anæsthetic flush and of partial anæsthesia is a little wider. Two series of histamine punctures have been laid down along the borders of the anæsthetic area; the flushed area remained unchanged in extent.

In three cases of urticaria factitia we have similarly anæsthetised the skin of the interscapular region, subsequently firmly stroking the skin along a line passing right over the anæsthetised area. The results are as follows: redness appears along the whole line of stroke and this is followed by whealing; but in all instances the wheal has been decidedly less prominent where the anæsthetic area is crossed; in one case it scarcely appeared. Where the anæsthetic flush is slight, it may be seen that no additional flush develops round the red line on the anæsthetic area. Histamine, punctured into these anæsthetic areas yields reduced wheals, as in the case of normal skins.

To sum up, thorough and superficial anæsthetisation of the true skin abolishes the flush which surrounds the histamine puncture, small burns, and a line of stroke in urticarial cases; both histamine and stroke wheals developing upon these areas are of reduced size, but this reduction is presumably associated with increased vascularity of the skin upon which the stimulus is put down; the presence of an anæsthetic flush detracts from the value of the observations, so far as the reduction in the size of the wheal is concerned. It is also to be stated that these observations become of greater value when viewed in combination with those now to be described. Standing by themselves, doubt may be felt as to whether they illustrate anæsthetisation of the nerves to their very end branches.

Cases of nerve degeneration. Four cases of old standing nerve injury arising out of war wounds have been examined. In three of these cases the ulnar nerve had been divided near the elbow; in each case the characteristic muscular paralysis was associated with complete anæsthesia of the ulnar border of the hand and wrist and of the little finger and part of the ring finger. In the third case the median nerve had been cut, and had left paralysis of the corresponding muscles and an area of complete anæsthesia involving the ventral surface of the thumb and of the index finger and a portion of the palm of the hand. In all three cases at the time of examination the area of anæsthesia had been stationary for several or many years. The following statements, except when mentioned to the contrary, apply to all four cases.

(a) The vessels of the arm were occluded for 3.5 minutes and released. A general hyperæmia followed and this spread uniformly over the anæsthetic and æsthetic areas of skin.

(b) Several histamine punctures (1 in 3,000), were laid down quite symmetrically on the two hands, both congested by throwing pneumatic pressure upon the upper arm. On the insensitive side, the site of puncture was in each instance marked by a small bright red spot, a few millimetres in diameter; on the sensitive side, a bright flush of several centimetres diameter appeared. Thus on the anæsthetic side dilatation of arterioles was confined to the region directly influenced by histamine. Owing to the tests being made for the most part on the skin of the hand, whealing was usually very slight or moderate in amount; the whealing when distinct (2 cases) was equal on the two hands; the histamine punctures were put down as near to the border of the hand or wrist as possible.*

(c) The arms being first congested, the circulation was occluded and histamine punctures were laid down symmetrically. Purple spots soon developed around the site of puncture in three out of the four cases, and were alike in size and appearance on the two hands.

* Whealing being better marked on the skin of these parts.

(d) Procedure (b) was repeated in 3 cases, substituting repeated strokes with a blunt point for histamine punctures. In two cases red lines were alone produced on the sensitive and insensitive side; in the other two cases the red line soon became surrounded by a spreading flush on the normal side, but none appeared on the anæsthetic side.

(e) With the arms congested as in (b), the ends of two test tubes containing boiling water were repeatedly applied for equal and short periods to symmetrical areas. Local reddening was produced on both hands, but this was always surrounded by a spreading flush on the normal hand, never on the anæsthetic hand.

To sum up, the hyperæmia which follows release of an occluded circulation is not noticeably influenced by nerve degeneration. Bier⁷ has already shown that it occurs when all the nerves to a limb have been freshly cut. This hyperæmia seems to be independent not only of a reflex spinal arc, but also of a local nervous mechanism; the same statements and conclusion apply to the *local* hyperæmia produced by histamine, strokes and heat. In contrast with the local reaction is the behaviour of the surrounding erythema; this does not occur in the denervated skin, whether the stimulus takes the form of histamine punctures, stroking or burning. Lastly, whealing of the skin to histamine is uninfluenced by degeneration of the nerves.

Freshly divided nerves. We have been unable to obtain cases of sensory nerve palsy arising from recent wounds and have therefore resorted to a method described by Trotter and Davies³². If the forearm is searched with a faradic current issuing from a pointed electrode, the course of these nerves for a short distance from the point at which they immerse from the deep fascia can be determined accurately. These courses are marked on the skin and one or more of the nerves is selected and paralyses by an injection of 2 per cent. novocaine and 1 in 100,000 adrenalin. So accurate is the faradic method that the nerve can usually be touched with the point of the injecting needle and an injection of a few c.cm. of anæsthetic yields a complete paralysis lasting several hours. A protocol of a single series of observations made in all essentials with the same result upon the arms of each of us will sufficiently illustrate the method and our findings.

The cutaneous branch of the musculocutaneous nerve, and the adjoining branch of the internal cutaneous nerve were anæsthetised by separate injections of 2 or 3 c.cm. of adrenalinised novocaine about 4 cm. below the elbow joint. The greater part of the skin of the front of the forearm became completely anæsthetic, this anæsthesia extending almost to the wrist in front and beyond the radial border of the arm to the posterior aspect of the wrist. The area was outlined and the lower part of it, well away from the site of injection,* was used for observation. The anæsthesia lasted several

* An essential precaution when adrenalin is used in the injection: the object of the adrenalin is to prevent quick absorption of the anæsthetic.

hours. A slight but just perceptible flush appeared over parts of the anæsthetised area and quickly faded away again. Thermopile readings then showed the temperature of the skin to be equal on the two sides within a small fraction of a degree centigrade.

(a) The effect of occluding and releasing the circulation were not tested on this arm; it was tested in the second subject and gave the expected result, namely, a uniform hyperæmia.

(b) Two groups of 3 histamine punctures were laid down symmetrically on the arms, the veins being congested to 50 mm. Hg. previously. Flushes extending for several centimetres in all directions from the punctures appeared on the two arms. They were equal in extent and brightness and equal wheals subsequently appeared on the two sides.

(c) Two similar groups of histamine punctures were laid down symmetrically on the arms after congesting them and occluding the circulation. Purple spots in the immediate vicinity of the punctures developed equally on the two arms; on releasing the circulation equal and widespread flushes appeared, and subsequently equal whealing was seen.

(d) Procedure (b) was repeated, substituting for the histamine stimulus, 10 firm superimposed strokes. Local red lines, quickly surrounded by a flush, 3-4 cm. in diameter, developed on both arms; and both lines of stimulation subsequently showed whealing. The whealing was a little greater on the æsthetic side, otherwise the reactions were identical. Repeated on another part of the arm two hours later, equal flushes and equal wheals were obtained. (The second subject showed equal whealing on the two arms in similar circumstances.)

(e) With the veins of the arms congested to 50 mm. Hg., the arms were symmetrically heated with test tubes of boiling water. A local red reaction, accompanied by a vivid and extensive surrounding flush, appeared equally on the two arms. The reaction was repeated later with identical results.

(f) Scratches 6 or 7 cm. long with the point of a needle were made symmetrically on the two arms. Fine red lines appeared and were soon surrounded by flushes of about 3 cm. diameter. Eventually the lines of scratch developed definite wheals. The appearances were quite similar on the æsthetic and anæsthetic arms.*

While carrying out these observations, our colleague Dr. K. S. Hetzel injected into his own forearm a dose of 1 c.cm. pituitrin solution in connection with his own observations. He told us that as a result he had developed a patch of anæsthesia on his arm and kindly allowed us to make observations upon it. The arm was examined 3 days after the injury and an area of complete anæsthesia outlined about 5 cm. below the site of the injection and

* This test was not repeated on the second subject, the space available being insufficient.

evidently due to the injection having hit a nerve trunk. The area was 6 cm. long and about 2 cm. broad. We congested this arm and tested it with 4 histamine punctures; the reaction to these punctures included widespread flushes and well developed wheals, equal in every respect to those appearing on control skin of the same arm. Stimulated with hot test tubes, the usual central redness, surrounded by a widespread flush, appeared equally on the anæsthetic and æsthetic skin. On the 14th day after the injury the area of anæsthesia was unchanged; ten superimposed strokes were put down on it and on control skin; equal and widespread flushes developed around the local red lines. On the 21st and 22nd days the area was again examined and the anæsthesia found to be unchanged; a hyperæsthetic area now bounded it. Altogether 5 histamine punctures were put down at intervals on the anæsthetic area, the arm being first congested, and an equal number on control skin. Those on the anæsthetic skin all showed central and bright red spots immediately around the punctures, but no trace of surrounding flush; the control series presented the usual widespread flushing. The wheals of the two series were well developed, in fact unusually large, but equal. On the 23rd day the temperature of the anæsthetic skin was found to average 32.2° , that of a neighbouring area 31.9° ; two groups of 3 closely set histamine punctures were put down on these two areas, on the former the temperature subsequently rose 0.4° and on the latter 0.5°C. , an inappreciable difference. Testing the arm with heat, only a local redness appeared on the anæsthetic area, but was surrounded on the control skin by a bright and widespread flush. Ten firm and superimposed strokes gave a corresponding result, a local red line on the anæsthetic area, a red line surrounded by a wide flush on the æsthetic area; slight and equal whealing followed along both lines. Occlusion of the circulation was followed on release by a bright hyperæmia affecting anæsthetic and æsthetic areas equally. Thus, in the fresh stage the reactions to histamine (3rd day), burn (3rd day), and stroke (14th day) were quite normal; on the 21st to 23rd days, a sufficient time having elapsed for degeneration to occur, the flushes surrounding the points stimulated in each of these several ways failed to appear, the remainder of the reaction in each case presenting no appreciable change.

To sum up, on areas rendered anæsthetic by distant and fresh nerve section the reactions to histamine puncture, to burning and to repeated stroking or to scratching, each of the last two being sufficiently potent to produce whealing, are identical with those produced on normal skin. We particularly emphasise the intactness of the surrounding flush developed by all these forms of stimulation. These flushes, one and all, fail in skin in which the nerves have degenerated or in which the skin is adequately anæsthetised locally. All these flushes are fundamentally alike; they seem to be identical in nature with those observed by Breslauer⁸ to follow the application of mustard oil, in that they are all independent of reflexes through the central nervous system; they are all produced by a local reflex mechanism, similar to that described by Bruce⁹ in the conjunctiva.

Comment.

Reviewing our conclusions to this point, we have seen that the reactions of the skin to stroking on the one hand and to histamine puncture on the other are threefold. (a) An independent local vasodilatation caused without the intervention of the nervous system. (b) An independent and widespread dilatation of the arterioles, dependent upon a local reflex. (c) An independent and local change in the permeability of the vessel walls, which, like the local vasodilatation, is uncontrolled by the nervous system. The reactions in the case of stroke and histamine, those most fully compared, appear to be identical; the reactions to other injuries, such as burning, show similar resemblances.

The total reaction of the skin, though of this complexity, is the same for two apparently distinct classes of stimuli, mechanical and chemical. We may with some confidence add a third class, the thermal stimulus which, if pressed, also leads to whealing: though the reaction to this stimulus has been less extensively examined. Such being the case the presence of a common factor of causation in the reactions arising from the several forms of stimulus inevitably suggests itself.

Simply to compare the reactions to stroking and histamine, to show them to be similar or different, has not been our sole purpose. We hoped that the histamine reactions, if similar to the stroke reactions, might throw light on the latter. Those observations which appear to us to do so and which seem to bring us nearer the common factor are now to be described, and we shall come shortly to the chief thesis of our paper.

EVIDENCE OF THE RELEASE OF A HISTAMINE-LIKE SUBSTANCE
IN SKIN INJURIES.

Susceptibility of urticarial patients to histamine and other substances.

It is clear that in urticaria factitia the skin is hypersensitive to stroking, responding by the production of wheals. This susceptibility of the skin might be peculiar to the stroke stimulus or it might be a more general susceptibility. The skin of 4 such patients (*Subjects 1 to 4*) has been tested against controls to determine this point, 1 in 3,000 and 1 in 30,000 solutions of histamine being used in each case. The preliminary vascular reactions and the ultimate wheals were no greater than those found in controls. In two patients we have also used morphia hydrochloride (1%), atropine sulphate (1%) and formic acid (10%), for these are also known to produce wheals when punctured into the skin^{29 & 31}; the resultant wheals were no greater than in controls similarly tested. We have also enquired of our patients as to their susceptibility to wheal in response to gnat bites and nettle stings;

they appear to react normally, though with variations similar to those experienced by control subjects, that is to say, healthy people who present no wheals on simple stroking. It may be stated here that there is some variation in the response of controls to histamine, and that similar variations are encountered in urticarial patients.

The susceptibility to wheal in urticarial cases proves to be a susceptibility peculiar to stroking and to similar mechanical injuries.* If the susceptibility in urticarial patients consists of an unusual reactivity of the vessels concerned, then the stroke and the histamine stimulus, producing as they do similar vascular reactions, would be anticipated to yield equally exaggerated reactions. In actual fact they do not; the reaction to stroking in urticarial patients is alone exaggerated. To put the matter more broadly, if we conclude, and it is difficult to avoid concluding, that the same complex mechanism is set in motion by two distinct forms of stimulus, but is set in motion by only one in an exaggerated fashion, then undue susceptibility of this mechanism in the urticarial patient is incredible. We come to the conception that for some reason a single stroke forms in the urticarial subject a more adequate stimulus to a mechanism, composed as it is of such nerve and vascular tissue elements as are involved, which is no more than normally excitable. Now since the stroke is a similar stroke to that which is put down on the normal arm and which, if unrepeatd, yields but a limited response, we are led to inquire if this stroke does in reality constitute the essential stimulus. This enquiry is answered and our conceptions are carried a stage further by the following observations.

Diffusible substances responsible for the local vasodilatation in normal and urticarial skins.

It has been customary to describe one of two local effects when the normal skin is stroked; light stroking yields a white line due to contraction of the capillaries and venules; heavier stroking produces a red line, due to dilatation of the same vessels. The first effect is probably ascribed correctly to stimulation of contractile elements (Rouget cells) lying on the walls of the minute vessels. The last has been interpreted as due to paralysis of these cells by the heavier stimulus. The natural reaction of involuntary muscle to mechanical stimuli is contraction; relaxation in direct response to a stronger stimulus of the same kind has not been convincingly described as far as we are aware. The reason usually given for the appearance of the red line cannot be regarded as entirely satisfactory therefore. Now it is notable that this red line when produced on the occluded arm does not

* One of our patients (*Subject 6*), however, was the occasional subject of spontaneous urticaria, a second susceptibility which may or may not be fundamentally identical with the first.

subside during the period of occlusion. So long as the circulation is stopped, the line persists at its maximal intensity (tested up to 25 minutes). This statement is true, whether the original stroke is heavy or lighter, providing that a red line appears. If corresponding strokes are put down on the unoccluded arm, the lighter of these fades away considerably during the same time intervals and is usually almost imperceptible at the end of ten minutes or less: similar fading is to be seen in the red line on the occluded arm after the circulation is released. These observations suggest that the stimulus producing the local red line persists with its full force throughout a period of occlusion, and that the line is not the direct result of the mechanical stimulus. While suggestive, there is an element of uncertainty in this evidence, since after fading the red line may reappear on a normal arm at a later period: until the meaning of this late reappearance is more fully understood, a positive conclusion cannot perhaps be drawn from the time periods of the first fading. The matter is placed on a much more definite basis by the next observations.

Spread of local skin reactions. If histamine (1 in 3,000) is punctured into a normal skin and the latter is closely watched for the first appearance of whealing, this will be found to follow the puncture usually in about $1\frac{1}{2}$ minutes. The diameter of the wheal at this stage is approximately 2 mm., but while it is growing in height during the next few minutes its diameter also increases. The following are examples.*

Time after puncture in mins.	Diameter of wheal in millimetres.		
	<i>R.G.</i>	<i>T.L.</i>	<i>Co.</i>
1	1.7	—	—
$1\frac{1}{2}$	2.0	2.0	2.3
$2\frac{1}{2}$	2.5	2.6	2.9
$3\frac{1}{2}$	3.0	2.9	3.1
$4\frac{1}{2}$	3.4	3.6	3.5
$5\frac{1}{2}$	3.9	4.0	3.7
$6\frac{1}{2}$	4.0	4.0	3.8
$7\frac{1}{2}$	4.0	4.0	3.8
$8\frac{1}{2}$.	.	3.8
10	4.1	.	.

* The results are similar whether normal or artificial subjects are used.

A similar spread, though of less extent, is seen in instances of stroke wheals in urticarial subjects. Thus :—

Time after stroke in mins.	Diameter of wheal in millimetres.			
Subject	1.	1.	2.	5.
1½	4.3	—	—	—
2	—	4.5	—	—
2½	5.0	5.0	4.0	5.7
4	5.1	5.2	4.3	6.1
5	5.0	5.2	—	6.0
7	—	—	—	6.7
9	—	—	4.8	6.9

Although the histamine and stroke wheals resemble each other in this respect, the resemblance is not necessarily of any great significance, for it may be argued that the fluid, gathering in the skin in both instances under some pressure, naturally tends to shift towards the sides. As in the resemblance between the degrees of whealing over different portions of the forearm, this may also be explained on simple grounds, and no light is thereby thrown on the nature of the processes involved in the production of the wheals.

Of much more significance from this standpoint are the following observations. The normal forearm is congested by placing an armlet on the upper arm and raising the pressure to 20 or 30 mm. Hg. : after a few minutes the pressure is abruptly raised to 200 mm. Hg. to occlude the circulation. At the end of a minute a series of histamine punctures (1 in 3,000) is made into the skin. The punctured skin is lightly vaselined and the arm placed in water at 18-20° C.* Before long small purple spots appear at the sites of puncture : they quickly become more sharply defined and proceed to increase in diameter. The spots remain clearly defined and no wheals develop so long as occlusion continues : but if at any stage of the observation the armlet pressure is released and the skin is warmed, wheals quickly appear, and the diameters of these wheals when they are first sufficiently defined to measure correspond accurately to the diameters of the purple spots which they replace.

Thus, although the circulation in the arm is brought to a standstill, the area of capillaries and venules dilated locally by histamine notably increases ; the diameter increases by about 2 millimetres (doubling itself) in about 8 minutes. Moreover, the area over which the walls of the minute

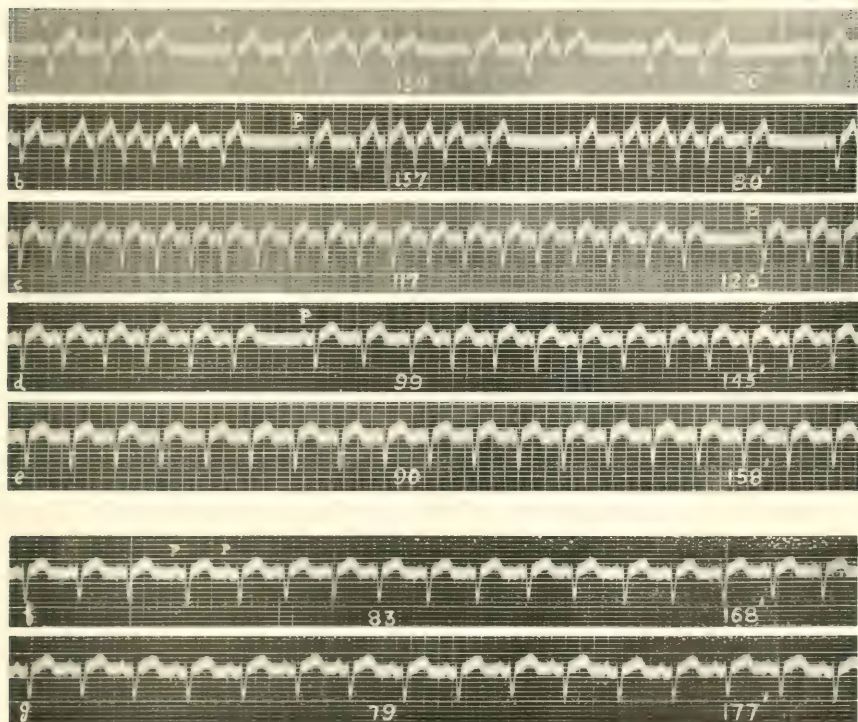
* The reason for employing the cold bath, as will be seen later, is that it preserves such permeability of the vessels as is produced.

Time after puncture in mins.	Average diameters of purple spots in millimetres.		
	<i>R.G.</i>	<i>T.L.</i>	<i>Co.</i>
2 $\frac{1}{3}$	1.0 approx.	2.0	2.0
3 $\frac{1}{3}$	2.7	2.0	2.4
4 $\frac{1}{3}$	3.0	2.8	2.8
5 $\frac{1}{3}$	3.0	3.1	3.1
6 $\frac{1}{3}$	3.0	3.1	3.3
8 $\frac{1}{3}$	3.5	3.5	3.7
10 $\frac{1}{3}$	3.8	4.0	4.0
Arm released; size of beginning wheals	3.8	4.0	4.0

vessels develop increased permeability enlarges correspondingly. The diameter of the wheal, measuring this when it first appears, depends upon the length of the occlusion. There can be little or no doubt as to the meaning of this reaction. Histamine is forced into the skin along a needle track and, when the circulation is at a standstill, it diffuses in every direction and, to judge from the almost circular shape of the spots, almost equally through the surrounding skin. Some such spread no doubt occurs in the skin in which the circulation is free, for wheals developing in these circumstances cover an area which is greater than the area actually damaged by the needle or originally contaminated by histamine; but, as we have seen, this spread may be attributable, in part at all events, to shifting of the fluid gathering under pressure. When gradual and seemingly regular spread of the local* vascular reaction occurs in the occluded arm, simple diffusion of the poison is alone adequate as an explanation.

A similar encroachment upon the surrounding skin is noticed in the case of the local vascular reaction which follows stroking in urticarial subjects. The observation is carried out as for the histamine puncture, the arm being congested and its vessels occluded. After an interval of a minute or more the skin is firmly stroked. The borders of the purple line which develops are accurately marked by inking the skin, and ink lines are lightly ruled on the skin across the line of stroke to mark the points for measurement; the skin is vaselined and laid in cold water (16-18°C.), and the measurements proceed. We include a few representative examples from different subjects in the accompanying table. The spread of the red line is evident without measurement, for it encroaches upon and sometimes passes the lines inked at its original margins. In some instances after spread has occurred it is

* As opposed to that which is reflex.



Figs. 1 and 2. Portions of long curves taken at frequent intervals to illustrate the effect of a single dose of 0.6 of a gramme of quinidine (see Table III). The curves *a* to *g* were taken 20, 80, 120, 145, 158, 168 and 177 minutes, respectively, after the dose. The curves traced successively show lengthening of the paroxysm and slowing of the paroxysmal rates from 158 to 83. The last strip *g* shows pure normal rhythm.

In these and the remaining curves the time is in fifths of a second and the ordinates are cent. (1 millivolt).

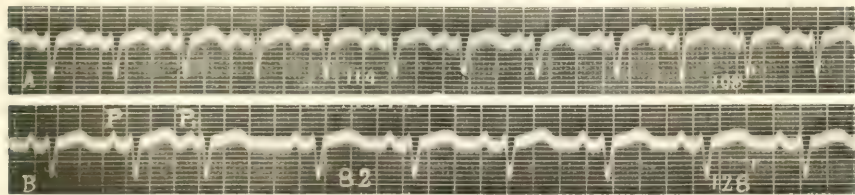


Fig. 3. Two strips of curves from a previous series of observations (see Table II) taken at a faster rate, to display the difference in the form of the paroxysmal and normal auricular deflection. The first strip *A* shows a continuous paroxysm at a rate of 114, taken 108 minutes after a single dose of 0.6 of a gramme of quinidine. Strip *B*, taken 20 minutes later, shows normal rhythm interrupted by a single extrasystole, *P'*.

Time after stroking in mins.	Av. diam. of purple line in millimetres.				
<i>Subject</i>	<i>1.</i>	<i>1.</i>	<i>2.</i>	<i>3.</i>	<i>5.</i>
2	4.7	4.0	4.0	—	4.1
3	—	—	—	3.75	4.1
4	5.0	4.5	4.0	—	4.3
5	—	—	—	4.0	4.3
6	7.2	5.0	4.3	—	4.3
7	—	—	—	4.0	4.4
8	8.0	5.5	4.7	—	4.4
9	—	—	—	4.3	4.6
10	9.7	5.7	5.0	—	4.7
12	—	6.7	5.0	5.5	4.8
Arm released : size of beginning wheals ...	7.7	7.0	5.5	5.5	—

still possible to define the original borders ; the colour of the central parts of the line is a trifle darker, the recently opened vessels contain blood which is a little more oxygenated, for it has lain a lesser time in contact with the tissues. As in the case of histamine, the wheals, when these first appear on releasing the arm, have much the same diameter as have the corresponding purple lines at the instant of release ; there is spread, not only in the area of dilated vessels, but also an increase in the area of relatively permeable vessels.

The table shows a definite spread in the cases of the last three columns (*Subjects 2, 3 and 5*) : it was much more conspicuous in the case of the first column (*Subject 1*) and associated with this is the fact that this patient is our case of most conspicuous whealing. On his skin, the purple lines at the end of the occlusion were somewhat less sharply defined at their edges than in the other patients ; it was also noticed that the margins of the wheals, subsequently developing, exhibited a similar lack of marginal crispness, rendering their measurements a little less certain. In the case of this patient, amongst others, we have adopted a control procedure. One arm is treated as described, being occluded for 10 minutes, while the other is stroked simultaneously without occluding its vessels. The wheals subsequently appearing on the occluded arm presented diameters averaging 7.2 millimetres ; those on the unoccluded arm averaged 5.1 millimetres and were notably crisper at their edges ; the measurements were made in both instances at the time of the wheal's first appearance.

The spread of the vascular reaction to stroking in the occluded limb of urticarial subjects, and the widening of the area of relatively permeable vessels which goes hand in hand with it, is to be interpreted as similar or

identical in origin to the parallel phenomena observed in the histamine reaction. The comparison is important because in the last case, we have introduced a diffusible substance into the skin, because we expect diffusion to occur during the period when the circulation is at a standstill, and to exhibit itself by creating a more widespread reaction. The parallelism supports the view that in the line of stroked skin a diffusible substance, having a similar local action to that of histamine and producing vasodilatation on the one hand and increased permeability on the other, is liberated. The suggestion is also compatible with the following further observations. If we choose the arms of non-susceptible subjects and stroke these, after congesting them and after occluding their vessels and proceeding in other details in a fashion similar to that described, the purple lines appear; but as the occlusion is continued, the diameters of these lines do not appear measurably to increase and wheals do not appear when the arms are released. The following observations (first three columns) undertaken simultaneously with those on histamine and tabulated on page 230, are sufficiently illustrative. Assuming a diffusible substance to be liberated by stroking, the absence of perceptible widening of the vascular reaction in the non-susceptible subject is to be explained by its liberation in insufficient quantity; the absence of ultimate whealing is correspondingly explained; for spread of the vascular reaction on the hypothesis suggested requires diffusion of enough substance to raise its concentration to a level in the surrounding skin adequate to produce a vascular reaction. In the last column of the same table is given the result of repeatedly stroking one of these relatively non-susceptible arms. In this instance the vascular reaction spreads and on releasing the

Time after stroke in mins.	Diameter of purple lines in millimetres.			
	<i>R.G.</i>	<i>T.L.</i>	<i>C.</i>	<i>C'</i> (10 strokes)
1½				4.5
2½	3.3	3.2	3.8	
3½	3.3	3.2	3.8	4.75
4½	3.3	3.2	3.8	
5½	3.5	3.2	3.8	5.5
6½	3.5	3.2	3.8	
8½	3.5	3.2	3.8	
9½				6.0
10½	3.5	3.2	3.8	
12			—	6.5
Arm released; size of beginning wheals ...	none	none	none	6.2

circulation whealing occurs. The last example is parallel in every respect to the reaction in an urticarial subject, and the observation differs only in the necessary repetition of the stimulus. If we assume that the stroke liberates a diffusible substance in the urticarial subject, we must assume that it does so also in the normal subject, but that it is liberated in insufficient amount to produce whealing unless the stimulus is a repeated one.

We next proceed to examine the flush along somewhat similar lines.

The flush is due to a chemical stimulus.

When histamine is punctured into the skin, a surrounding erythema or flush appears in about 20 seconds, spreads and reaches its height in about 3 or 4 minutes and subsequently begins to fade away. The flush surrounding histamine punctures in an urticarial skin is not perceptibly brighter nor more extensive than is that similarly produced in a normal skin. A similar and extensive flush is seen around the line of stroke in urticarial subjects and around the line of stroke in normal subjects if stroking is repeated. The similarity between the flushes which surround a histamine and a stroke wheal, and the similarity of their time relations, suggests them to be of similar nature. In both instances, as has been shown, the flush is due to a local reflex. When a histamine puncture forms the stimulus, the flush might be ascribed either (1) to the immediate stimulus of the prick alone, for a simple prick also produces a surrounding flush in both normal and urticarial subjects, or (2) to the introduction of the poison alone. It is easy to show that the first is not true, since the flush surrounding the site of a histamine puncture is brighter and far more extensive than that surrounding the site of a simple prick in the same case. The flush surrounding a histamine puncture might also be supposed (3) to arise in part from the stimulus of pricking and in part from the action of the poison. The appearance of a flush around the site of a prick on the normal skin is insufficient evidence that the pain stimulus of pricking can by itself induce a flush even in a normal skin. Obviously there is the alternative explanation that the prick, by damaging the tissues, liberates substances which themselves awaken a vascular response: that is a question to which we shall return presently. Apart from its more extensive character, clear evidence is forthcoming both in normal and in urticarial cases that the greater part if not the whole of the flush surrounding a histamine puncture is due to the action of the poison. Briefly this evidence consists in showing that the fading of the flush can be deferred by occluding the blood vessels to the affected skin. If a group of three closely set histamine punctures (1 in 3,000) is laid down on the skin of a forearm, the flush soon appears, spreads, becomes more vivid and then begins to fade. The manner of fading is of interest: small pale areas appear at first in the outermost parts of the flush and later nearer its centre; these coalesce and small detached areas of flush are left, themselves fading in

colour and gradually diminishing in size. It is not an easy matter to time accurately either the first sign of fading, or the actual end of the flush; but it can be ascertained very readily in most subjects that fading is far advanced within 10 minutes of the laying down of punctures. If a similar group of histamine punctures is laid down on a forearm the vessels of which have previously been occluded, and occlusion is maintained for a further period of ten minutes or more and the arm then released, the whole arm at once becomes brightly hyperæmic.* The general hyperæmia shortly begins to fade from all parts except the neighbourhood of the histamine punctures. As it lessens, the flush surrounding these punctures becomes clearly defined; it is then standing at its height, being equal in extent to that seen on the unoccluded arm, and its fading away can be followed stage by stage. If two arms, one subsequently occluded for 10 minutes and the other unoccluded, are stimulated simultaneously, the fading of the histamine flush on the unoccluded arm is far advanced before that on the occluded and released arm begins. In other words, the occlusion postpones the dying away of the flush. In practice it is actually found that the fading of the flush on the occluded arm is a little slower than that on the unoccluded arm, but the comparison is not quite a fair one, since the one arm has been occluded and the other has not; their condition during the period when fading is occurring is not quite the same, the occluded arm becoming the cooler. To compare more accurately the time relations of fading on the two arms, the following method has been adopted and used upon a number of subjects. The vessels of both arms are occluded for a given period of time, usually 11 minutes. One minute after occlusion, a group of three histamine punctures is laid down on one arm; the occlusion is continued for 9 minutes, when a group of histamine punctures is laid down symmetrically on the second arm;† occlusion is continued again for 1 minute, and the arms are simultaneously released. Now the arms have been treated in a precisely similar fashion except that on one a group of histamine punctures has been laid down 10 minutes and on the other 1 minute before its release. The general hyperæmia fades away and the histamine flushes become defined simultaneously on the two arms, and their borders are simultaneously marked by lightly inking the skin (usually 3 minutes after the release). A few minutes later the borders of the flushes are again simultaneously outlined. In marking out the borders of the flush on the second occasion, any completely detached portions are neglected, the area of continuous flush being alone included for the sake of simplicity. After a further interval the outlines are again marked, and finally the times at which the last and central remnants of flush disappear are

* The so-called "reactive hyperæmia" which always follows the release of a previously obstructed circulation.

† In using one arm to control the other in this and similar observations, it is a matter of moment to determine that they are of equal temperature and that they wheal equally; otherwise the second arm is not a fit control.

noted. We then possess two diagrams such as are shown in Fig. 3 and can compare them. The values set against the contours represent the corresponding times from the release of the circulation (the values in brackets represent the times which have elapsed since the punctures were put down). Corresponding contours (right and left) naturally vary from each other in form and somewhat in extent, one way or the other; but in general it may be stated that they are remarkably alike. The fading on each arm occurs simultaneously; it also occurs in the same fashion, namely, by the appearance of mottling, which is at first confined to the outer parts of the flush; using the method described, it is not possible to decide from the appearances of the two arms, at any stage following the release, which was punctured first. The delay in the fading of the flush on the arm first punctured is delayed precisely by that period of the occlusion, which falls between the puncture of one arm and the other; that is so whether the interval is 5, 10 or 15 minutes. The meaning of this delay is evident. The histamine which is punctured into the arm at an early stage of the occlusion is retained there, and so long as it remains and acts, the arterioles of the flushed area stay open.* It is inconceivable that the flush which remains on releasing this arm is due in any part to the original mechanical or painful stimulus of pricking. A reflex vasodilatation so caused would subside with equal or almost equal quickness whether the arm was occluded or not; its action would not be delayed or continued, by the time period of the occlusion. The delayed fading of the flush shows very conclusively, if such evidence is required, that the reflex flush is provoked by histamine and not by the prick.

This conclusion may not seem to possess intrinsically any great importance. It becomes important when it is applied. If we find that stopping the circulation for fixed periods of time accurately delays any vascular flush, such as might otherwise be supposed to arise from a mechanical stimulus, we may place such a mechanical stimulus out of court as the direct cause of the flush, and thus obtain a proof that the immediate cause is a chemical stimulus, of a nature similar to that which obtains in the case of the histamine reaction.

For this reason we have repeated our observations, now using urticarial subjects and stroking the skin, with keen expectancy that we should obtain decisive evidence, one way or the other, in respect of the central problem of our studies. The flush which develops around such strokes behaves in precisely the same way as does that surrounding histamine punctures, as

* The vessels are relaxed throughout the period of occlusion around a histamine puncture; if the vessels of the arm are not only occluded but the veins are also slightly congested, a very faint shadow of what will subsequently form a bright flush is sometimes visible. A similar observation has been made by Carrier and Rehberg (*Skand. Archiv f. Physiol.*, 1921-2, *At-vi*, 250) in the case of the flush surrounding strokes. In both instances however this phenomenon seems to point to active and reflex dilatation of the *minute skin vessels*, rather than the arterioles, though the last are no doubt involved likewise.

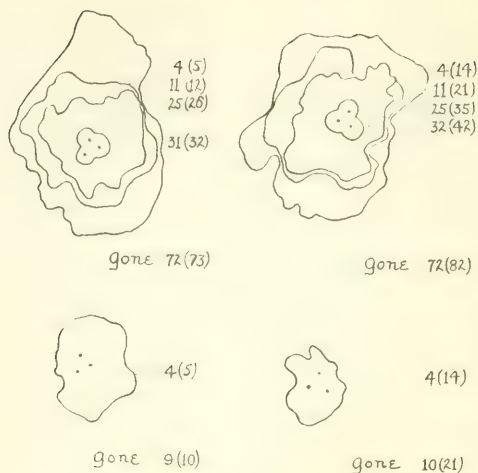


Fig. 3 ($\times 2/3$). Normal subject. In this and the succeeding two figures, the left outline corresponds to a left arm area and the right to a symmetrical right arm area of skin. The vessels of both arms were occluded; a group of three histamine punctures (1 in 3,000) (above), and a group of three simple pin pricks (below) was put down on the right forearm 1 minute after the occlusion and on the left forearm 10 minutes after the occlusion. The occlusion of each continued to the 11th minute, when both arms were released. The outlines of the flushes, aroused by the stimuli, were outlined at fixed times after the release of the vessels and these times are expressed in minutes against the corresponding contours. The numbers in brackets represent the corresponding times elapsing after the stimuli were laid down. The times at which the flushes disappeared completely are also noted. The positions of the punctures are also shown.

we know from repeated tests upon a number of urticarial patients. The contours of fading show the parallelism previously described (Fig. 4); the fading occurs in the same fashion, namely, by the appearance of pale areas which gradually coalesce.

In an earlier part of this section the possibility was discussed that the flush which comes around a simple pin prick may be due, not to the pain stimulus of the prick, but to damage of the tissues and to the setting free of substances in the tissues which themselves directly determine the flush. Evidence for this is obtained by the method here described and is illustrated

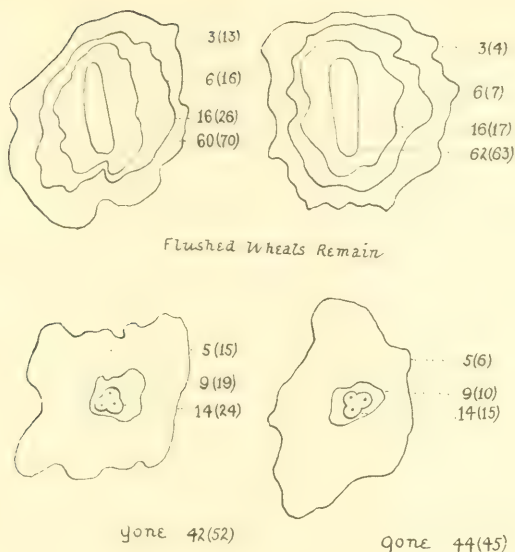


Fig. 4 (· 2 3). *Subject 2, urticarial.* The vessels of the two arms were occluded. One minute later the left forearm was stroked (above), and a group of three histamine punctures (1 in 3,000) was laid down (below); at the 10th minute, or 9 minutes later, the right forearm was similarly and symmetrically treated, both arms being released at the 11th minute. The contours of the flushed areas are shown as these fade away. In the stroke figures, the fading was followed until the flush confined itself to the wheals.

in Fig. 3. The fading of the pin prick flush is postponed by stopping the circulation in the limb, and it is postponed by precisely the period of time intervening between the pin prick and the release of the arm.

A similar statement applies to the spreading flush which follows excessive heating of the skin. If a test tube containing boiling water is laid on a small area of skin until a stinging heat is felt, and this stimulus is repeated half a dozen times in quick succession, the skin is not only reddened over the immediate area of contact, but over a wide area around. As has been shown, the outside flush is due to a reflex arteriolar dilatation. If this form of stimulation is applied to an arm in which the vessels are occluded, and this

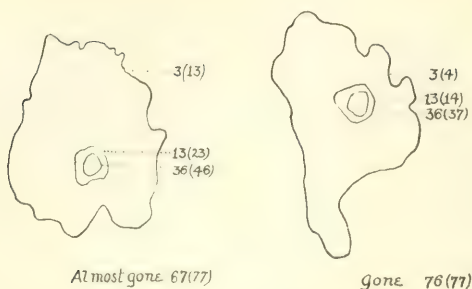


Fig. 5 (· 2/3). Normal subject. The vessels of both arms were occluded, the left arm at 0 minutes and the right at 9 minutes. At 10 minutes, the arms were burnt equally and symmetrically over small areas. At the end of the 11th minute of its occlusion each arm was released. The contours of the flushes as these faded are shown at corresponding periods of time after the release. The central contour on each side approximately corresponds to the area originally heated.

occlusion is maintained for a number of minutes, the fading of the flush is postponed by that period of time (Fig. 5). In carrying out this observation we have not occluded the two arms simultaneously, but have occluded the one for 1 minute and the other for 10 minutes and have then heated the two simultaneously; otherwise it is difficult to apply equal stimuli to the two arms. Each arm is released at the end of its period of 11 minutes' occlusion, and the time of fading charted. Apart from the fact that the outlines are not drawn simultaneously, these charts may be read in the same fashion as those previously used as illustrations.

To sum up, it is to be concluded that the flush which surrounds an urticarial wheal, a simple pin prick, or a burn of the skin is in each case due, not to a direct stimulation of a local nervous mechanism and to a reflex vasodilatation arising therefrom, but to substances released in the skin by damage of the tissue elements; these flushes are all produced in a fashion fundamentally the same as that which is produced by the introduction of histamine into the skin.

In contrast to the delaying effects which obstructing the circulation has upon the flushes of histamine, burns, etc., is the absence of such an effect upon the local redness produced by temperatures of about 43°C . If the two arms are occluded and immersed in water as follows:—

		<i>Rt. arm.</i>		<i>Lt. arm.</i>
2 mins.	..	43°	..	33°
6 mins.	..	33°	..	33°
2 mins.	..	33°	..	43°
2 mins.	..	33°	..	33°

and the arms are then withdrawn and released, both became universally hyperæmic. When this hyperæmia fades away, the hyperæmia produced by heat is seen on that which last experienced the heat (the left): on the other (the right), little or no trace of heat hyperæmia is seen: or if a heat hyperæmia is at first perceptible on both arms, it fades to imperceptibility on the right arm about 8 minutes earlier than on the left arm. When an arm is immersed in the hot water in this experiment it should be immersed to a marked level and held quite still; and it should be immersed more deeply in the cooler water. The local redness produced by mild heating is apparently not due to the liberation of vasodilator substances, but seems to be a more direct effect, as it has usually been thought to be. The illustration is perhaps of most value here in showing that vessels of the skin if dilated by a cause which is not persistent, decrease in size again after a suitable interval of time, whether the circulation is stopped or not.

To return to the stroke reaction; it has now been shown that three independent parts of this reaction, namely, the local vasodilatation, the surrounding reflex vasodilatation and the œdema can none of them legitimately be attributed to the mechanical stimulus. In the first and third case there is evidence that a diffusible substance is liberated in the skin and yields the local dilatation and œdema; in the second case we have evidence that a chemical substance is liberated and yields a widespread arteriolar dilatation through a local nervous mechanism. It is unnecessary to postulate more than one substance to explain the triple reaction. Further evidence that increased permeability is a response to a chemical stimulus is provided by the following experiments.

Effects on the wheal of occluding the vascular supply, and of variations produced by heat and cold in these circumstances.

An armlet is placed on one upper arm of an urticarial subject and the pressure in it is raised to a point far above the systolic pressure; the two arms are firmly stroked and two series of histamine punctures are laid down also on symmetrical areas. On the unoccluded arm, stroke and puncture yield the usual wheals within three or four minutes; on the occluded arm no trace of wheal is to be seen, and this is so even if the occlusion is prolonged

for 25 minutes. If, however, the pressure is released at the time when the wheals have developed on the control arm, they quickly develop on the released arm also. These facts have been referred to already; but in carrying out the observations other important points have come to light. If the occlusion is carried beyond a certain period of time the wheals which develop on release are reduced in size; if the occlusion be very prolonged whealing fails. The time relations vary considerably. In some subjects occlusion for 5 minutes is sufficient completely to prevent the appearance of the wheal which normally follows stroking, in others and more usually longer periods of time are required. Not only is there a variation from subject to subject but there is considerable variation in the same subject from time to time. Similar statements apply to the histamine wheal, with this difference only, that in general a longer occlusion is required to abolish a 1 in 3,000 histamine wheal than a stroke wheal in the same case. It was in investigating the effects of occlusion upon histamine wheals on our own arms that we first noticed this variability, and it has been submitted to prolonged investigation. One of the first factors considered was room temperature, but no relation to this could be found within such limits as 16° and 26° C. We thought that the amount of blood left in the occluded arm might be varying and occluded the arm quite abruptly from a large pressure reservoir, with the arm held vertical or after congesting it to various points. We also considered the possible effects of previous exercise upon the condition of the limbs: but from none of these sources could we derive the information required. On one day a 10 minute occlusion has resulted in the complete failure of the wheal, on the next or more distant day, the observation has been carried out in a precisely similar fashion in so far as time of day, previous exercise, room temperature and the degree of venous engorgement were concerned, and the same length of occlusion has seemingly been without material influence on the ultimate size of the wheals. We greatly desired to obtain a constant method of preventing wheals developing. Ultimately skin temperature, as opposed to room temperature, was found a chief cause of variation, and we began to obtain constant results when the limbs were immersed in water at given temperatures.

Effects of heat. If histamine (1 in 3,000) is punctured into an occluded arm and this is soaked for 3-8 minutes in water at from 43-45° C., on drying and releasing the arm much reduced wheals or no wheals appear. When satisfied that this reaction was constant in three individuals, we began to investigate the question further in an attempt to analyse more precisely the reason why the wheal fails. Our procedure was first of all as follows. The arm being occluded and remaining occluded for 1 minute, three groups of histamine punctures (1 in 3,000) were laid down on the ventral skin of the forearm in the relative positions shown in the accompanying diagram. These three may be termed *A*, *B* and *C* respectively. All three groups were

now quickly and thinly coated with vaseline* and the arm placed in hot water obliquely, so that the water was along the line marked *I* in the diagram. The arm lay in this position for a suitable period, varying from $1\frac{3}{4}$ to $2\frac{1}{2}$ minutes, and was then brought upright so that the water lay along line *2* in the diagram; immersion then continued for another period varying from $1\frac{1}{2}$ to 2 minutes. The precise times and temperatures to suit a particular arm are ascertained by trial. The arm is withdrawn, dried lightly and released. Large wheals develop in group *A* and, if suitable temperatures are employed, the wheals are definitely reduced in size in group *B* and are still more reduced or absent in group *C*.† Now all groups are upon skin which has been deprived of its circulation for a given time and all experience a hyperæmia on release, the hyperæmia derived from occlusion itself.‡ Two groups have been heated and both show reduction, one group has been heated longer than the other and shows greater reduction; both these groups subsequently show the hyperæmia of heat when the arm is released. If one group alone is heated, only that group experiences the subsequent hyperæmia produced by heat, and it is possible that this hyperæmia might tend to prevent the full development of wheals subsequently. It is for this reason that we have immersed both *B* and *C* in hot water, though for varying times, so that both groups might subsequently experience the heat hyperæmia.

On a few occasions, however, we noticed that the subsequent heat hyperæmia over group *C* was a little more intense than over group *B*, and this discovery necessitated a further precaution. It will presently be seen that if the arm is occluded, punctured and soaked in cold water, the wheals are preserved. Our next step therefore was to repeat our observations in the same fashion, but finishing by soaking all three groups in cold water (13-16 C.) for 5 minutes before releasing the armlet (line *3*).§ This bath of cold water prevents the arm from developing any appreciable subsequent hyperæmia, due to previous heating, and renders the conditions under which the wheals of groups *B* and *C* actually develop more completely similar. The results are the same as previously described, full wheals in group *A*, reduced wheals in group *B* and much reduced or absent in group *C*. The only difference in the treatment of groups *B* and *C*, from first to last, is the heating of *C* for approximately 4 minutes, and of *B* for approximately 2 minutes. Yet this difference of treatment usually produces a clear or conspicuous difference

* Our first observations of this kind were made without this precaution, but on subsequently testing the effects of soaking a developing histamine wheal in water we sometimes thought we could detect a slight effect upon it; our observations were therefore repeated as here described, and in all subsequent immersion experiments (including those previously described in other sections) we have consequently used vaseline to keep the skin dry throughout the observations.

† If the immersion of group *B* is too short, no certain difference between it and *A* will be detected; if it is heated too long it will be found in the same condition as *C*.

‡ Such influence as this hyperæmia may exercise is discussed at a later stage.

§ It is also advisable further to immerse the arm in water at body temperature for a minute before the actual release, otherwise goose skin often develops from the cold water and the comparative size of the wheals may then be difficult to judge.

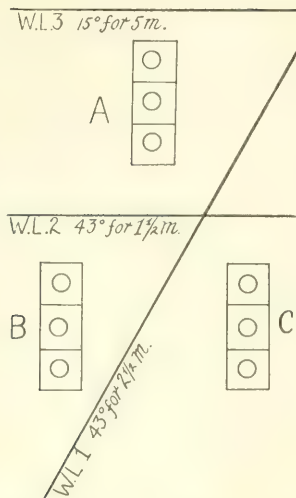


Fig. 6. The squares are marked on the arm beforehand; the circles indicate the points subsequently punctured.

in result. That the difference in the sizes of the ultimate wheals is due to the different temperatures at which they are maintained, *during the period of occlusion*, and that it is not due to the *after effects* of such temperatures at the release of the circulation, is proved by repeating the experiment and puncturing histamine into areas *B* and *C*, not after the occlusion, but just before the circulation is released. Equal and prominent wheals then appear in the two areas, although such after effects of heating, as may be supposed to persist, are fully experienced. It is of interest to note in the main experiment that if the final immersion in cold water for 5 minutes does not include group *A*, this series of wheals is exposed to room temperature (about 20°C.) throughout and, having its vascular supply cut off, usually displays reduced or much reduced wheals ultimately; the relative effects in groups *A* and *B* are, of course, unchanged in this variant of the experiment. We have tested the effects of occlusion and warming at 33-36°C. in a similar way and find the wheals are reduced or prevented by it, though to a lesser extent than with the hotter water.

The effects of cold. After occluding the limb, and at the end of a minute puncturing in the histamine, group *C* is immersed for 5 minutes in water at 12°-13°C. Groups *B* and *C* are then immersed in water at 38° for 2

or 3 minutes and the arm dried and released. The largest wheals develop and these are full in group *C*, those of group *B* are much reduced or absent, having been exposed to room temperature for 5 minutes and to 38° for 2 minutes: the wheals developing in group *A* which have been exposed to room temperature throughout are intermediate in size.

A variation of the experiment testing the effects of heat and cold is the following. Groups *B* and *C* are placed at a wider interval from each other, namely, near the radial and ulnar sides of the arm and, after occluding the circulation in the usual way, the arm is pronated and the radial side carrying group *B* is brought under hot water at 43° for 2 minutes, while mops of cold water (at 18°) are applied constantly to group *C*. At the end of 2 minutes, groups *B* and *C* are immersed for 5 minutes in water at 18° . The arm is then supinated and its ulnar side carrying group *C* is immersed in water at 43° , while mops of water at 18° are applied to *B*. Both are now soaked in water at 18° for 2 minutes, the arm is then placed in water at 37° to avoid subsequent goose skin and the wheals allowed to develop while it is immersed. At the end of the observation the groups have been treated as follows:—

		<i>B.</i>	<i>C.</i>
Occluded		43° 2 mins.	18° 2 mins.
		18° 5 mins.	18° 5 mins.
		18° 2 mins.	43° 2 mins.
		18° 2 mins.	18° 2 mins.
Unoccluded. . . .		37° until wheals develop fully.	

The wheals of the two groups develop equally, both sets being reduced. This fact confirms the view that heat affects the reaction when it is applied and not through its after-effects, namely, heat hyperamia at the release, which is slightly present in the case of group *C* while negligible in group *B*. The observation also excludes different effects of heat at the beginning and end of a period of occlusion; it has been repeated on several subjects, heating sometimes the radial side and sometimes the ulnar side of the arm first.*

Thus it is shown that, the circulation being occluded, wheals subsequently developing are reduced in size or wheals fail to develop and that this effect is assisted by high and hindered by low temperature: the temperature effect, occurring as it does during the period in which no blood is flowing in the arm, forcibly suggests chemical action.

Stroke wheals. The effects of occluding the circulation and maintaining the arm at hot or cold temperatures on stroke wheals are the same as upon histamine wheals. Our observations have been carried out on four urticarial subjects, and we have used both the histamine and stroke stimulus in these.

* A necessary precaution, since wheals do not always develop quite equally on the two borders of the limb.

Thus if the observations illustrated by Fig. 6 are repeated with histamine on an urticarial case, results identical with those already described are obtained. If simultaneously with these histamine punctures strokes are laid down, each one parallel and near to a group of punctures, the two sets of reactions (for histamine and stroke) may be obtained in one observation and the sets compared. But this simultaneous method is not often satisfactory since the amount of heating required to reduce a stroke wheal is usually less, sometimes conspicuously less, than is required in the case of a histamine wheal (1 in 3,000). To cite an exceptional case, and using the reference letters of Fig. 6, the arm of an urticarial subject was occluded for 1 minute and histamine punctures made in the usual three skin areas (*A*, *B* and *C*); alongside each group two short firm strokes were put down. *C* was soaked in water at 43° for 5 minutes; *B* for $2\frac{1}{2}$ minutes; all were now immersed at 18° for 5 minutes and finally for 2 minutes at 36° and the arm released. Over *A*, three slightly reduced histamine wheals and two slightly reduced stroke wheals developed; over *B*, three much reduced histamine wheals and two reduced stroke wheals developed; over *C*, there was but a trace of histamine and stroke wheals. Usually, however, this quantity of heating reduces the stroke wheals at both *B* and *C* so much that little or no appreciable difference can be found between them. To obtain stroke wheals of three sizes, water of lower temperature must usually be used (*i.e.* around 38°) and, during the heating of *B* and *C*, *A* must be kept cool. By suitably arranging the temperatures during the period of occlusion, wheals varying from a full size down to nothing can be obtained. Thus, parallelism again appears between the histamine and stroke reactions: and an interaction between a released substance and the tissues during occlusion, in the case of stroke stimuli, is suggested as the cause. Arising out of these experiments there are further observations which are described and discussed in the following sections.

Loss of increased permeability and the condition of refractoriness. When a stimulus (histamine or stroke) is put down on an occluded and heated arm which is subsequently cooled, the frequent failure to wheal on release is due to disappearance of the originally increased permeability of the vessel walls. We make the statement in this form because, if the release of the arm comes at an earlier stage and before heat is applied, whealing does occur. When it occurs it begins almost as soon as the circulation is released, showing that the vessels have increased permeability at the time of release; in this it contrasts with a wheal produced on the unoccluded arm; in the latter there is a very considerable interval ($1\frac{1}{2}$ minutes or more) between the stimulus and the beginning of whealing: this is the period during which permeability is increasing. Thus, in the occluded and heated arm, the vessels affected by the stimulus at first develop the usual increased permeability: but as the occlusion is continued, and especially if the arm be kept hot, this passes away. Now, it is not possible to attribute the failure of the wheals to a simple decline of the vascular reaction as a whole for, *even when wheals fail, a*

vascular reaction is present. Throughout the whole period of such occlusion the purple spot of histamine, or the purple line of stroking, remains in undiminished intensity on the arm, and, so soon as the general hyperæmia which follows the release has subsided, a *full* flush is seen surrounding the area stimulated. These observations have been confirmed repeatedly in the case of both forms of stimulus. The failure to wheal is decidedly not due to previous decline in the vascular dilatation. In Part I of these reports evidence is brought to show that increased permeability of the vessel walls in the case of stroke wheals is largely independent of vascular dilatation. In an earlier part of the present report we promised to bring further evidence of this, and further to support the same conclusion for both the histamine and stroke reactions. This evidence has now been given; it is clear that neither the local nor the reflex dilatation, even when these are fully developed and acting in combination, will provoke a wheal; and it is evident that increased permeability is separable from the rest of the vascular reaction.

When we found that a histamine wheal fails to appear on an occluded and heated arm, we at first thought that the tissue poison might have diffused away or might have been destroyed by the tissues in contact with it; but further observation and reflection rendered this conception untenable; it is inconsistent with a persistent vascular dilatation. It is particularly inconsistent with the appearance of a full flush and with the precise delay in the fading of this flush (by the time interval which intervenes between the puncture and the release of the arm). This has been described already; but it is to be added here that the delay is similar and precise whether wheals develop or not: a statement which applies to both histamine and stroke reaction.

Some diffusion of the histamine does occur, as has been shown; but this diffusion is only to a little distance and is insufficient to account for the effects observed. We interpret this delayed fading as due to retention of active histamine *in situ*; the failure to wheal, therefore, must be due to change in the tissue element concerned, the vessel wall no longer responding to histamine by developing its usual enhanced permeability. Now this supposed unresponsiveness can be tested directly, by repuncturing the original places with histamine. The procedure is as follows. Two series (Fig. 7, *A* and *B*) of histamine punctures (1 in 3,000) are laid down on the skin, the arm being first occluded. The arm is now heated for 5-10 minutes and subsequently cooled; or, alternatively, the occluded and punctured arm is maintained in a bath at 33° for 15-20 minutes;* the results are very similar. Immediately before the arm is released one series (*B*) is repunctured and a fresh series (*C*) put down on the neighbouring skin. The new punctures on *B* should fall as near as possible to the old punctures, and to this end the sites of the first punctures are dotted with ink on the arm. After releasing the arm, little or no trace of wheals is seen over *A*; over the control area *C*

* The last method has the advantage that on release no heat hyperemia can occur.

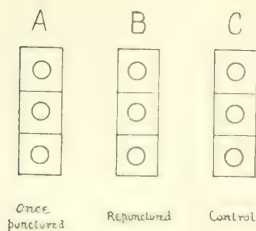


Fig 7.

wheals develop. Over *B* (the unpunctured group) little whealing is seen: although a little more whealing occurs here than at *A*, the effect is much slighter than over *C*: and this despite the fact that the repunctured areas now contain a double dose of histamine. On some occasions the whealing on the repunctured group has been so slight as to be imperceptible.* Thus it is shown that the areas which originally failed to wheal will not wheal appreciably even if fresh histamine is introduced. A lesser or greater degree of refractoriness is demonstrated, and the reason why whealing originally fails to occur in response to the original dose of histamine, which presumably is still held in the skin at the release, seems clear.

It is here to be observed, however, that the wheals which develop over the control areas *C* are smaller in size than are wheals following simultaneous punctures on a symmetrical area of the other arm, which has been neither occluded nor heated. This reduction of the control wheals, though it complicates our reactions, does not render them unanalysable. Its meaning will be discussed at a later and more appropriate stage.

Now, in so far as the demonstrated refractoriness of area *B* is concerned, a simple change might be held responsible. The original punctures produce a local engorgement of the vessels and increase the permeability of the vessel walls. It is possible, if not probable, that much of the plasma held in these vessels, when stagnation first occurs on occluding the vessels, passes out into the tissue spaces, though it is naturally insufficient in quantity to produce perceptible oedema of the skin. If that were the case the red blood cells would be left closely packed as a viscous mass in the capillaries. It is conceivable that owing to this viscosity, stagnation continues after the blood stream is released and that the apparent loss of increased permeability and the state of relative refractoriness is due to the vessels being choked.

*The whealing which appears in repunctured spots is greater if the new dose is applied a minute before the release, but it is still much less than that occurring on the control area.

If the purple spots are watched at the release, they are seen to redden at once: but this reddening is due to filling of the venules of the subpapillary plexus with arterial blood. There is no doubt that the stream is at once re-established in these venules; it is not quite so easy to show that it is re-established in the overlying capillaries. To show that the phenomena are not due to stagnation in the capillaries is of importance, providing that it is held that the fluid of a wheal is derived from the capillaries only. This is itself very doubtful; but so long as it is unproved that the collecting and subpapillary venules also pour out fluid, the condition of the capillaries in a refractory spot must be taken into account. We have repeatedly examined by Lombard's method the condition of the purple spots at the end stage of occluding and heating the arm, and have demonstrated that the blood is easily displaced from the venules by slight pressure: the pressure required to displace the blood from the capillaries is, however, considerably greater, enough to suggest stickiness of the contents. We have also watched these spots microscopically during the release of the circulation. The colour of the area as a whole becomes at once arterial, and we believe, but we are not certain, that the colour of the capillary loops alters simultaneously with that of the venules. On several occasions blood movement in the capillaries has been witnessed and an immediate repuncture of a neighbouring and similarly conditioned spot has proved this to be refractory; but it is not possible to ascertain that the circulation is at once restored in all or even many of the capillaries in the circumstances of the experiment. To settle the question we have resorted to another and more decisive method. An Esmarck's bandage is firmly wound over the whole arm, held vertically, and the Riva-Rocci armlet is placed immediately above it on the arm and pumped well beyond systolic pressure. The Esmarck bandage is now removed and a completely blanched arm is exposed. The histamine punctures are laid down at marked points and the occluded arm is heated at 43°C. for 6 to 10 minutes, cooled for 5 minutes at 18°C., and finally warmed at 36° for 2 minutes to take off the chill.* A few seconds (or a minute†) before releasing the circulation, series *B* (Fig. 7) is repunctured and a control series (*C*) put down. The results are very similar to those previously described; wheals develop over *C*: over *A* little or no trace of whealing is seen; over *B* there may be little or no trace of whealing, though more usually these wheals are a little greater than on *A*, but definitely less than on *C*. The signs of refractoriness are perhaps somewhat less well displayed, though they are definite, when the Esmarck bandage is used. Now if, before releasing the circulation, one of the punctured spots of series *B* is brought under the microscope, no blood is to be seen in any of its capillaries or venules, but the instant the arm flushes the capillaries and venules surrounding the visible punctures in the

* These observations have also been carried out on occluded and punctured arms maintained at 33°C for 15-20 minutes. The results are similar.

† If put down 1 minute before, all the resultant wheals are larger than when put down a few seconds before release, but the order of size is unaltered.

skin fill. It is clear therefore that the loss of increased permeability and the presence of relative refractoriness of the skin, where it has previously been punctured, cannot be explained on the ground that fresh blood is unable to enter and flow through the capillaries, but that it is due to some other cause. In view of the possibly less conspicuous results obtained when the Esmarch bandage is employed, a viscosity effect as a minor contributory cause cannot be excluded altogether. If the refractoriness were due to loss of fluid from the blood during the period of stagnation, it would also occur when the occluded arm is kept cool; that is not the case.

The phenomenon of relative refractoriness, presuming we have correctly interpreted it, is clearly one of interest and importance; we have not, however, been able to accumulate sufficient evidence of its nature to justify us in discussing it at length. It seems to us probable that such refractoriness to histamine, produced by a previous injection of histamine, is to be explained on the basis of an interaction between the poison and the tissue cells governing permeability. In this connection we may cite the very interesting observation of Straub³⁰ on the action of muscarine upon the aplysia heart. He finds that muscarine acts only while it is passing into the muscle cells and that once these cells are saturated with muscarine the action of the original dose and of further doses fails.* In our observation, there is an obvious and close relation between refractoriness on the one hand and the actual loss of pre-existing permeability on the other; it is suspected that these may be part and parcel of the same fundamental reaction, though in the absence of proof, it is perhaps desirable that they should be kept as separate concepts. The tissue cells concerned in the interaction are held to be the cells of the vessel walls, for the state of permeability is the part of the reaction involved. Given that we are so far right, then we should be justified in anticipating that the interaction would show some degree of specificity. In the case of histamine, it is naturally a purely chemical interaction that we have in view.

Most conveniently we may argue in the converse direction. Allowing that occlusion and heating by a similar process prevents the appearance of wheals, ordinarily provoked by a distinct form of stimulation such as stroking, and supposing that we find that the areas on which stroke wheals should have appeared but do not appear are now relatively refractory to histamine, this demonstration would form presumptive evidence that underlying both histamine and stroke wheal is a very similar or perhaps an identical chemical reaction in the cells of the vessel wall. Now this is precisely what we do find. If a firm stroke is laid down on the arm of an urticarial subject, and the arm is heated sufficiently and occluded sufficiently long, no wheal develops at the release; and if histamine is punctured into

* Underhill and Epstein³¹ have also described an observation which may be relevant; they find that pilocarpine at first increases the permeability of the vessel walls, as evidenced by a concentration of the red blood cells, but that immediately afterwards, saline introduced leaves the blood stream less readily than before pilocarpine was introduced.

the line of the stroke, a little before or soon after the release, the line proves refractory to it. A customary result is a complete absence of whealing; in a few instances there is slight whealing, but it is never so great as that which is produced by simultaneous control punctures on the neighbouring skin. The apparent refractoriness of the old line of stroke provides another opportunity of excluding stagnation in its vessels as the reason why a wheal fails to appear. If the observations are repeated,* substituting Esmarek's bandage for simple occlusion, results similar to those already described are still obtained. It is naturally to be asked if the possible substitution of histamine for stroke and stroke for histamine form a complete series. We have seen that the histamine spot will become refractory to histamine; we have seen that a line of stroke will become refractory to histamine. Can a histamine spot be shown to become refractory to stroking, and a line of stroke to stroking? The answers to these questions are both affirmative, but in each instance the reaction is not easy to obtain.

In an urticarial subject, two small neighbouring areas are chosen and into each, while the arm is occluded, six closely set histamine punctures are made, so that the areas affected may be larger than usual. One of these areas of histamine puncture is kept as a control. If a wheal develops upon it, the observation as a whole must naturally be repeated in modified form. The arm is now occluded and heated in the usual way, until a sufficient time has elapsed to prevent the appearance of histamine wheals on release. At the release a firm stroke is drawn across one of the two sets of histamine punctures. When a successful reaction is obtained, the stroke gives a conspicuous wheal, broken in its centre where it crosses the area rendered refractory by histamine. Now the reaction is difficult to show for this reason. Stroke wheals are in general more sensitive to interferences than are histamine wheals. It usually requires more heating and a longer occlusion to abolish the last than the first. Often it seems impossible completely to prevent the histamine wheal from developing. Moreover, as we have seen, if a stimulus is put down on the otherwise undamaged skin of an arm which has been occluded and kept warm or heated, the wheal does not develop fully; in these circumstances a stroke wheal is usually less well developed than a histamine wheal. Consequently, what usually happens is that it is impossible to obtain a stroke wheal of reasonable size on an arm in which histamine areas have been rendered refractory by occlusion and heating. The reaction described can only be shown in suitable patients, namely, those in whom fairly prominent wheals can be obtained by stroking at the end of a period of occlusion and heating sufficient to prevent the original histamine wheal from developing; it can be shown only if the period of occlusion and heat is carried just to the requisite point and, seemingly, if the final stroke is laid down near the end of this period. We

* Or the arm is kept occluded and at 33° for a longer period.

have witnessed the reaction, nevertheless, in perfectly unmistakable form on a number of occasions.

In an urticarial subject the skin of the occluded arm is firmly stroked and the arm heated for a period known just to prevent a wheal subsequently appearing and, immediately before the release, the arm is again stroked across the original line. In successful reactions the first stroke produces no trace of wheal, the second stroke yields a somewhat reduced wheal which is broken, or less conspicuous, where it crosses the original line. This reaction is even less easy to obtain than the last, in part for similar reasons, but in part for reasons not clearly understood. We have failed to obtain it satisfactorily much more often than not. A parallel reaction and one which is probably caused in a similar fashion, may be obtained without difficulty. If a stroke wheal is raised on the back of an urticarial subject and is watched, the edema eventually subsides; during the later stages of this process, fresh stroke wheals which run across the old line are broken or reduced at the crossing points. To best display these breaks light should be thrown very obliquely on to the skin, so that the wheals cast shadows; the breaks, however, are in general indisputable.

These observations as a whole reiterate the parallelism between histamine and stroke wheals. They lead us, providing we accept the view of refractoriness here supported,* to the view that underlying the stroke wheal there is a chemical reaction common to both. It is to be mentioned, however, that refractory stroke lines are not only refractory to histamine, but that they are almost if not equally refractory to puncture with 1% morphine hydrochloride, a poison which like histamine also raises wheals on control skin. This fact does not contradict our view, since we may explain the action of morphia as we explain the action of the stroke: both produce tissue damage.

When a small area of skin from which the blood supply is cut off is rendered refractory by the puncturing in of histamine or by stroking, this state of refractoriness does not persist for long periods of time after the circulation becomes re-established. There is usually a fairly prompt recovery; thus 5 or 10 minutes after the release, histamine punctured into a refractory stroke line often produces small wheals, and after longer intervals it produces more fully formed wheals. The time required for recovery is, however, variable from subject to subject. The same phenomenon is observed after release, when histamine is repunctured into spots originally rendered refractory by histamine puncture. We attribute recovery to the gradually restored metabolism of the cells affected. When wheals fail to appear at the release of a heated and occluded arm, it is not very infrequent to observe, in the absence of further interference, their appearance in reduced form after an unusual period of delay, namely, 15 minutes or

* It is necessary to be dilident in expression, owing to the complexity of the factors involved; when we speak of refractoriness we mean in general relative refractoriness. Absolute refractoriness is either rare or difficult to prove.

more.* This spontaneous and delayed appearance of a wheal is the exception and not the rule in the case of stroke wheals: it is more frequent in the case of histamine wheals, and can be explained by supposing that some of the irritant liberated in or introduced into the skin remains. But if we adopt this explanation it does not seem possible to accept Straub's muscarine experiment as a strict analogy: since it is necessary to assume that the circulation restores the reactivity of the vessel wall cells while these still lie in contact with the substance which originally rendered these cells refractory.

As has been seen, areas punctured with histamine or stroked become refractory quickly when the circulation is stopped and the skin is heated to 43-45°, but heating is not essential: the areas become more slowly refractory if lower temperatures are employed, similar effects being shown at natural arm temperatures (33°). On the one hand while the act of heating expedites its occurrence, it is not the cause of refractoriness: on the other hand, obstruction of the circulation has not necessarily anything to do with its production: it is possible to regard circulatory obstruction as merely displaying an existing refractoriness by keeping fluid from exuding during the initial period of increased permeability. If the circulation is intact whealing quickly follows a stroke stimulus: the wheal forms fully within a period of about 5 to 8 minutes and then ceases appreciably to develop. Such periods are not very different from the minimal periods required for a stroked area to become refractory when the skin has its circulation stopped and it is kept at body temperature. Looking at the matter from this standpoint, it is difficult to avoid considering that refractoriness, and the state of relative impermeability of the vessels which accompanies it, is at least in part responsible for the ending of transudation in uninfluenced wheal formation. In some part this ending may be due to dilution of the substance provoking it by the outpouring of vessel fluids, in part it may be due to gathering pressure in the wheal or to diminution of the vascular reaction; though if we may judge of the last by the curve of skin temperature (Fig. 1), the full blood supply to the skin, where the wheal stands, long outlasts the maximal point of skin swelling. The idea that occlusion is not essential to the onset of the refractory state but rather that the last may be merely displayed by the first, is supported by the observation that in the line of a wheal obtained on the skin in which the blood supply is intact, refractoriness to further stroke stimuli during the later stages of the fluid's absorption can be demonstrated.

The points here left in doubt require further work to elucidate them: they do not affect our main thesis.

Formation of miniature craters. An interesting phenomenon is frequently observed when histamine is punctured into an occluded arm which

* In many of these instances there seems to be a very slow and continuous growth of the wheal for 15 or 20 minutes after release.

is subsequently heated. We have previously stated that, if this occlusion and heating is sufficiently prolonged, no wheal appears. If less prolonged a miniature crater develops; that is to say, while no wheal develops in the immediate neighbourhood of the puncture, a minute ring of œdema appears around the central point and at a radial distance of about 2 millimetres or a little more. The phenomenon is due to the interplay of two events, refractoriness of the tissue and diffusion of the poison. The histamine is put down centrally and spreads radially and gradually. The tissues near the centre, during the period of occlusion, are longer in contact with histamine than are those into which diffusion eventually occurs. The vessels of the central portions lose their permeability and become refractory while histamine is still spreading into fresh tissues at the margin; if at this stage, the circulation is released, whealing occurs in the form of the minute border ring described.

A parallel phenomenon is sometimes to be observed in the case of stroke wheals, developing in similar circumstances. In this instance, however, the stimulus has affected a narrow band of skin. On this no wheal develops, but two little parallel ridges of œdema mark the outermost borders of the reaction.*

Effects of simple heating reconsidered.

In an earlier part of this paper the effects of heating the skin of the unoccluded arm upon subsequent wheal formation have been described, and we have learned that such heating conspicuously reduces the size of the wheal formed in these circumstances, or actually prevents whealing. When we saw this effect in the case of the histamine wheal we naturally concluded that the histamine, being punctured into an arm in which the skin circulation is greatly increased, is washed away† before it can act; and this conclusion seemed to be substantiated by observing that if the histamine is laid down a minute or a little more before heat is actually applied, full or almost full whealing occurs, the interpretation being that in these circumstances the histamine could interact fully with the tissues before the increased blood flow to the skin affected it. If this natural interpretation were valid it would also be valid in the case of stroke wheals, seeing that these behave similarly, and the observations would provide a powerful argument that a substance is formed in the skin of urticarial subjects when these are stroked. But later observations showed that heat applied to an arm in which the circulation is occluded also prevents or reduces subsequent whealing. It became conceivable that heat applied without occluding the vessel might act similarly, namely, by rendering the tissues concerned refractory in the sense previously

* It is to be noted that the border œdema in the stroke reaction is simulated sometimes by the actual forcing of the natural tissue fluids to the sides when a heavy stroke is put down.

† It is unnecessary to discuss the alternative possibilities, namely, absorption by blood vessels, or washing out by increased lymph flow.

described. We have been at pains to show that in the occlusion experiment, the immediate effect of increased temperature is to expedite the reaction and have suggested that occlusion may in itself be without much influence, other than to display refractoriness once this has occurred. If we are to use the effect of heat applied to the arm in which the circulation is intact as evidence that increased blood supply washes away histamine or a corresponding substance, it is necessary for us to show that the effect as we have described it is dependent upon an active circulation and is not due to refractoriness of the skin. To do this we first use histamine (1 in 3,000 or 1 in 30,000) in the following way. The arm of a normal or urticarial subject is immersed in water at 44° to 45° C. for 3 minutes. The circulation in it is now occluded and 3 histamine punctures (*A*) are laid down on the hot skin; the arm is returned to the water and at the end of 1 minute the circulation is released; three more histamine punctures (*B*) are now laid down at once and the arm again placed in the water for 1 minute. At the end of this time it is immersed in a bath at 16-18°C.* and the wheals are allowed to develop fully.

The difference between the treatment of the two series of histamine punctures and the end results may be expressed as follows:—

<i>A.</i>	<i>B.</i>
Punctures laid down on hot arm.	Punctures laid down on hot arm.
1 minute of occlusion and heat.	
1 minute of heat without occlusion.	1 minute of heat without occlusion.
Cooled.	Cooled.
Slightly reduced wheals develop.	Reduced wheals develop.

Series *A* has been subjected to 1 minute of heat while the circulation has been obstructed; otherwise the procedures are identical. Now we have seen that heat and occlusion combined tends to render the histamine punctured skin refractory. Series *B* possesses the advantage of escaping this influence. On the other hand, the histamine introduced in series *A* has lain in contact with the tissues, without the possibility of its being washed away for a period of 1 minute following its introduction. This advantage outweighs any that series *B* enjoys, and the result is the development of larger wheals in series *A* than in series *B*. We have repeated these observations in a number of subjects and in a variety of slightly different ways; it is in fact a perfectly easy observation to make. It shows decisively that when a wheal of reduced size appears on skin previously heated the reduction is in the main connected with an increased circulation. This demonstration permits us therefore to return to our original explanation, namely, that in the presence of a very active circulation histamine is carried away before it has time fully to react with the tissues.

* The reason for the cold bath will be seen a little later.

To complete the evidence it should be shown that stroke wheals are similarly influenced. That is also the case, though we have found it somewhat less easy to demonstrate. If the procedure described above is carried out, strokes being substituted for the histamine stimuli, both series of wheals (*A* and *B*) are usually reduced to mere traces and a comparison of size is unsatisfactory. Heat affects stroke wheals more decidedly than it affects histamine wheals. Lower temperatures (40 or 41°C.) are more suitable and the effects of such temperatures should not be prolonged, since there appears often to be some slight effect on the size of the wheal during the later stages. It is for this reason that the arm is removed from the hot water a minute after its release and cooled to check the further action of heat; in the case of histamine this is not necessary, though here also it renders the reaction a little more decisive. The observation in the case of stroke wheals must be carried out under more critical conditions; and the most decisive observations are made when the factors are modified a little to suit the particular patient employed. The optimum temperature may be a little higher or a little lower; the period of occlusion may require a little lengthening or shortening. By slightly varying the conditions we have not failed to obtain the same end result in the case of stroke wheals, already described for histamine, in any of three patients so tested.*

A further phenomenon is of interest and is compatible with the interpretation advanced, though it is seen inconstantly. When the wheals are developing while the arm is immersed in cold water, it is not infrequent to observe that the flush surrounding skin area *A* is more extensive and brighter than that surrounding skin area *B*; usually, however, the extent of these flushes is masked by the general redness of the skin. Now the flush is independent of the whealing and occurs whether the tissues become refractory or not; its extent, in the circumstances of the experiment, is perhaps a better index of the dose of histamine or other diffusible substance remaining in the skin at this stage, than is the eventual whealing.

If the failure of a wheal to appear on a previously heated arm is in the main due to loss of histamine in the one case and of a corresponding substance in the case of stroke wheals, as these observations strongly suggest, then it might be possible to show more directly that the wheal does not fail because the tissues have become refractory. The test is not, however, quite as simple as it might at first seem. A firm stroke is made on an urticarial arm previously heated to 45 or 46° for 3 minutes, and the arm is returned to the water and kept there so that no trace of wheal develops below the water line. Histamine (1 in 3,000) is now punctured into this line, and similarly, as a control, into unstroked skin beside the line. Frequently, in such circumstances, wheals fail to appear; they fail because the histamine has been punctured into a superheated skin. To obtain results from which a conclusion may be drawn, a patient must be chosen in whom previous heating affects the development of stroke wheals to a greater extent than those provoked by histamine. Two such patients have been tested. In the first reduced wheals of equal size,

* It will be gathered that on occasion we have failed to obtain decisive reactions in the case of stroke wheals, the wheals being seemingly equal; it is to be added that similar exceptions have been encountered in the case of histamine from time to time, though less frequently and usually when the weaker solution has been used.

An alternative method to that described is to occlude the two arms and to use symmetrical areas of skin; in the case of histamine this method suffices; in the case of stroke wheals it is less safe, since slight differences in the reactivity of the two arms is sometimes enough to confuse the results.

appeared in response to histamine on the line of stroke and upon the control area, as expected. In the second case the results conflicted; when the upper arm was used, the results were the same as those seen in the first case; when we employed the forearm, the histamine wheals were usually distinctly larger on the control area than upon the line of stroke. Our results, therefore, cannot be stated to show decisively that the factor of refractoriness is entirely negligible; though they are quite consistent with the conclusion that the main reason why reduced wheals result, when a stimulus is put down on superheated skin, is that the active circulation washes away the substance (introduced or liberated) before it can interact fully with the tissues.

In connection with the matter here discussed, one point of consequence to our previous experiments on refractoriness is to be noted. It has been seen that if a stimulus is put down on an arm showing heat hyperæmia, or if it is put down on an arm which shortly afterwards develops a heat hyperæmia, very reduced wheals develop if they develop at all. But if, when the stimulus is put down, it is at first guarded by occluding the circulation for a suitable period, the subsequent effect of a heat hyperæmia on release is, at all events in chief part, avoided. It is under the last conditions that our studies of refractoriness have been carried out.

Influence of reactive hyperæmia upon developing wheals, etc. In many of the observations recorded already a stimulus has been laid down on an arm during a period of circulatory obstruction. The release of the circulation is shortly followed by a bright hyperæmia of the whole arm (so-called "reactive hyperæmia"), and this is frequent while our wheals are developing. We have been careful to arrange our experiments so that the area studied and its control area shall be equally influenced by this hyperæmia; but a little more must be said to make it clear to what extent our results may be affected by it. It also remains for us to attempt to explain why, if control skin is stimulated near the end of a period of occlusion, the wheals developing are smaller than usual. These two questions are conveniently taken together.

If we soak both arms in water at 33°C. (normal skin temperature for the arm) for 15 minutes, occluding the left arm during the whole period and the right arm during the last 5 minutes of the bath, and if we lay down a group of 3 histamine punctures on each arm at the moment of release, the wheals developing on the left arm are smaller than those developing on the right arm. Now this effect has nothing to do with temperature, since both arms were maintained throughout in the same bath: it is due to one of two causes: (a) the longer previous occlusion of the left arm has produced a little refractoriness in the whole of its skin, or (b) the reactive hyperæmia, being of greater intensity and of longer duration in the left arm, washes away more of the histamine from this arm before it is able to act fully on the tissues. Supposing the last explanation is true, we ought to be able to guard the histamine from the circulation while it is acting by putting down the punctures, not at the release, but 1 minute before release. Wheals resulting from punctures put down 1 minute before release are always larger than those put down at the release in this experiment. It seems clear therefore that when histamine is introduced at the release, the reactive hyperæmia washes it away in part, just as does a heat hyperæmia; and since the hyperæmia

appearing on the left arm is more intense than that on the right arm, it is natural to expect smaller wheals on the former than on the latter. That however does not end the question, since of the two guarded groups (put down 1 minute before release) that which stands on the arm which has been occluded the longer yields wheals which are definitely smaller in size. Thus the question of refractoriness in this arm as a whole still remains open to us.

To test the matter further, we replace the warm bath by a hot one at 43-44°C. and proceed in a similar fashion, soaking both arms for 8 minutes, keeping the left arm occluded for the whole period and the right arm for the last 3 minutes only. Our object is to produce a heat hyperæmia in both arms at the release, so that inequality of the influence exercised by the reactive hyperæmia may, at the release, be reduced or abolished. The result of this experiment is similar to that in the warm bath. The groups of wheals laid down immediately at the release are smaller than those (the guarded groups) laid down 1 minute before release; but again the wheals are quite definitely and constantly less in size on the arm which has suffered the longer previous occlusion.

In view of these results, and while recognising that wheals laid down immediately at the release of an occluded and warm arm, are affected by the subsequent reactive hyperæmia, yet it seems clear that occlusion of the circulation in itself tends to produce a certain refractoriness of the whole skin which experiences it. Whether this general refractoriness is due to the release of metabolites in the asphyxiated arm and is by this means directly connected with the subsequent hyperæmia, is a question which may be left for future investigation. This speculation is in line with Anrep's explanation¹ of "reactive hyperæmia."

Some differences between histamine and stroke reactions.

In our comparisons between histamine and stroke reactions, the remarkable parallelism between the two has stood forth constantly. In almost every particular they are similar and are similarly influenced by various interferences. Such differences as we have found between them are quantitative, never qualitative; and of these three are chiefly notable. The spread of the local vascular reaction upon an arm during a period in which its circulation is at a standstill is usually greater in the case of histamine than in the case of a stroke stimulus. Occlusion and heat combined affects the subsequent development of a stroke wheal to a greater extent than it affects that of a histamine wheal. Lastly, a stroke wheal develops to a more notably reduced size than a histamine wheal, when these are provoked on previously superheated skin. The similarities are easy to understand if we acknowledge that, when the skin is stroked, substances are let loose from the damaged cells and that these have a histamine-like action. The differences here noted are also readily explained by the same theory. When the skin is stroked, such substances will be let loose in the neighbourhood of every

affected cell : that is to say, the substances are uniformly and intimately distributed. When histamine is punctured into the skin it is put down in a concentrated dose at one point. The three differences noted can all be explained as depending upon the way in which the poisons are distributed. Thus the spread of the vascular reaction is attributed to diffusion of the poison : as diffusion occurs to greater and greater distances, the concentration will fall. To produce a histamine wheal 4 millimetres in diameter, sufficient histamine must be introduced on the needle that, in adequate concentration, it may spread 2 millimetres in every direction. Following a stroke, the concentration may be only sufficient to produce whealing over the actual line of stroke and by diffusion a short distance beyond the actual lines of pressure. Similarly, in the case of the occlusion affecting the subsequent development of a wheal : in the case of a stroke reaction, substances let loose are at once in intimate contact with the tissues, whereas at first that is only so in the case of a histamine puncture at the actual site of puncture. Lastly, when the stimuli are put down on a heated arm, the whole dose of poison liberated by the stroke is spread over a large area and all the vessels of this area are involved in washing it away ; in the case of a histamine puncture the dose is introduced at one point and is caught by the vessels only as it diffuses to them, the puncture hole acting meanwhile as a reservoir.

The relation between the surrounding flush and the wheal reconsidered.

In Part I the remarkable association between whealing and the appearance of the reflex flush was briefly discussed, and it was pointed out that a greatly increased supply of blood to the skin is requisite to provide the fluids collecting in the stroke wheal within a few minutes. The association between flushing and whealing could reasonably be explained if it were found that the arteriolar dilatation, known to be present along the line of the wheal itself, was but a part of the general flush. Further observation has shown that this is not necessarily the case even when subsequent whealing occurs. Thus when histamine is punctured into a skin in which the nerves are degenerate and in which cyanosis has been induced by artificially congesting the limb, a bright red spot appears in the immediate neighbourhood of the puncture, though the surrounding flush fails. Thus, it seems evident that even when reflex dilatation of the arterioles is abolished their local dilatation is preserved *. This dilatation must be a direct as opposed to a reflex response. It matters not, so far as the formation of a wheal is concerned whether the response is direct or indirect, the necessary blood will be supplied ; consequently it is not surprising to find that wheals develop as fully on the anæsthetic as on the æsthetic skin. But the facts are opposed to the view which otherwise might be held, that *reflex* arteriolar dilatation is essential to rapid whealing.

* The vessels we have in mind are not those which are sufficiently large to have acquired a muscular coat, but the more terminal arterioles.

The notable association between these two phenomena is to be explained differently. When relatively small amounts of an irritant substance is released, as by stroking an insensitive skin, the concentration of the poison is sufficient to produce little more than a local vasodilatation. If the amount of irritant is larger it is sufficient to provoke an appreciably increased permeability of the vessel walls and at the same time so to stimulate the local nervous mechanism that it yields reflexly a widely spreading flush.

The observations so far recorded are those by which we were led originally to believe that when the skin is stroked or otherwise damaged, substances having a histamine-like action on the vessels and nerves are released, and that the reactions which follow are due to the irritant action of these substances.

While we have been inclined to regard the evidence which has been brought forward as sufficiently convincing, we have not failed to see that the theory would be materially strengthened if an irritant substance could be recovered from the tissue fluids. Tests for such a substance have been sought and amongst other methods adopted has been that of collecting fluid and puncturing it into normal skins.

Attempts to obtain wheals by puncturing wheal fluid into the skin.

Many observations have been made with a view to determining whether the fluid thrown out in the stroke wheals of urticarial subjects contain any substance which is capable, when introduced into a normal skin, of whealing that skin, and which might consequently be regarded as responsible for the original wheal.

A priori, negative results would be of little value: for supposing such a substance to be set free in the skin of an urticarial subject, it would at first be present in adequate strength: but the fluid collecting as the wheal forms would dilute it. The extent of such dilution might clearly be so great, as ultimately to render the wheal fluid seemingly inactive. If a small and measured quantity (about 0.5 c.mm.) of 1 in 30,000 histamine is forced into the skin (intradermally) the wheal which forms is large and, so we calculate, not less than 20 times greater in size than the drop of solution originally introduced. That means an ultimate dilution of not less than 1 in 600,000. There are the further possibilities that such a hypothetical substance might be destroyed or fixed by the tissues during the reaction.

Our procedure has been to drive capillary glass tubes into a stroke wheal, to withdraw small quantities of clear fluid, to place this freshly drawn fluid on normal skins and to puncture through it with a needle. The observations are complicated by the fact that in normal skins a needle prick penetrating the skin often produces by itself a minute wheal. It is necessary therefore to control the wheal fluid punctures by punctures through

similar drops of normal saline, or blood from the patient, laid down in the neighbourhood. We were encouraged to investigate the matter somewhat extensively by a preliminary observation. Small quantities of wheal fluid were taken from an urticarial subject, the first samples being taken 6 minutes after the stroke which provoked it and a later sample at 12 minutes. This fluid was punctured twice into the arm of one normal subject and four times into the arm of a second normal subject. In all instances distinct wheals developed: simple punctures on the same skins, and punctures through drops of the urticarial subject's blood, resulted in very small or inappreciable reactions. We have naturally attempted to repeat these results on subsequent occasions, but with indifferent success. The wheal fluids of 5 other subjects have been employed, and the punctures have been more numerous than in our first observations; the original subject has also been used again. A summary of the results is given in the following paragraphs.

Using *Subject 4* of the urticarial series (first observation) 6 wheal fluid punctures divided between two normal skins yielded 6 wheals, definitely larger than control punctures or control punctures through fresh drops of the patient's own blood. On a later day 24 punctures were made with wheal fluid, divided between two normal skins, and each controlled against saline punctures. Of these, 16 observations were indecisive, the wheal fluid and saline reactions being equal: 6 were positive, the wheal fluid yielding a greater reaction than the saline; 2 were negative, the saline exceeding the wheal fluid reaction. It is to be noted that the effects of punctures through saline were variable, a small wheal or none appearing. It is this variation of the simple reaction to a prick, which we have not been able fully to control, which renders comparison difficult.

Using *Subject 1*, 12 wheal fluid punctures into normal* skins, gave 3 positive results, and 9 in which wheal fluid and saline gave equal reactions.

Using *Subject 2*, 29 wheal fluid punctures into 3 normal skins yielded 5 positive and 3 negative results: in the remaining instances wheal fluid and saline punctures were equal. In this and the preceding two cases the fluid was withdrawn at various periods after the formation of the wheal, but there was no correlation between the interval and the positive reactions.

Using *Subjects 3 and 5*, 13 and 3 wheal fluid punctures, respectively, were equal to those given by saline in all instances.

Using *Subject 6*, 10 wheal fluid punctures, controlled against saline and against blood freshly drawn from the same subject, all gave positive results, the blood and saline reactions being equal and the wheal fluid reactions being constantly and perceptibly greater.

It is true that in two instances (*Subjects 4 and 6*), wheal fluid when punctured into normal skins has whealed these normal skins. In one of these cases, however, our attempts to obtain the reaction in the same constantly positive form were quite unsuccessful. In the remaining cases the results have been indecisive. The results as a whole are such as we should expect to obtain if the substances we seek were present in the fluid, but diluted by the fluid poured out to form the wheal to a point at which the concentration is barely capable of yielding outwardly perceptible effects.

The two normal skins used in these observations have been tested (amongst others) to find the minimal concentration of histamine required to produce whealing by the puncture method. For this purpose histamine in a given dilution of saline is punctured into a row of six points on the skin of the forearm, a parallel row of punctures being put down through normal saline.

* The same two normal skins have been used throughout.

We find that a histamine solution of 1 in 300,000 is clearly distinguishable and that a solution of 1 in 600,000 is also just distinguishable, from saline, if rows of punctures are put down in this manner; used in a concentration of 1 in 1,500,000, the effects do not differ recognisably from those of saline. We may say, therefore, that if such whealing as we have seen to follow the puncturing of wheal fluid into the normal skin, is in reality due to the presence of toxic substances in this wheal fluid, then the dilution of such substances expressed in the equivalent terms of histamine is in the average about 1 in 1,000,000. In fluids which produce whealing the concentration would be somewhat more; in those which seemingly produce none it might be somewhat less.

We desire, however, not to over-emphasise the actual results obtained, and will not go further than to state that while they seem perfectly compatible with the remaining evidence they lend some additional support, slight though it may be, to our conclusion that stroking the skin of an urticarial case releases a substance or substances in the skin which has a vasodilator action and increases the permeability of the skin vessels, the action resembling remarkably in these respects that produced by histamine. On the one hand it is conceivable that histamine is not the chemical substance directly concerned in the production of histamine wheals; its action may be similar to that suggested for morphia, it may act by poisoning the tissues and so releasing the essential substance or substances; in thus comparing it with morphia, however, it is to be remembered that the adequate concentrations of these two substances is very different. On the other hand, it is clear that we should not be justified in assuming, upon the evidence presented, that histamine is itself the substance released in the skin by stroking.

Discussion.

The first conclusions to which the observations discussed in the preceding pages lead us are for the most part already manifest, they are as follows:— that when the skin is mechanically damaged by punctures, by abrasions such as scratches, by heavy pressure as in stroking or where the skin is hit, the vascular reactions which follow are due directly to a local release of substances from the tissues so damaged. Similar or identical reactions are called forth, as we believe through the same chemical channel, by excessive heat such as is experienced in scalding and burning. Burns produced by ultraviolet light will almost certainly need inclusion in the same class. Similar and probably identical reactions are provoked by a variety of poisons, such as peptone, mustard oil and mustard gas, croton oil and other blistering fluids, morphia and atropine^{29 & 31}, and by such substances as are introduced into the skin by the bites of insects and by the stings of insects and of certain hairy plants, all of which substances may be regarded as tissue poisons. Certain bacterial poisons are probably to be added³¹. We refrain from placing histamine in the same list, though the reaction which it yields may be regarded as typical for all; and we so refrain because of the whole series histamine is

suspected to possess the closest chemical affinities to the hypothetical tissue substance which we have in mind as the ultimate stimulus.

Observation has seemingly gone sufficiently far to warrant the formulation of a more general law, namely, that every form of injury to the healthy skin reaching a certain grade of severity calls forth a series of nervous and vascular reactions immediately dependent upon the same fundamental and natural chemical stimulus. To put the matter in another way, it may be stated that there exists in the skin a single and organised mechanism of defence against injuries of all kinds and that the agent which alarms the garrison and mobilises the first forces of this defence is a chemical agent derived from the tissues. The perfection of this mechanism is such that the defence is immediately organised, and organised at every threatened point; it is arranged and carried through locally, being independent of higher centres of organisation (nervous) and of distribution (vascular).

The idea that substances liberated in the tissues are able to control the local supply of blood is no new one; it has been suggested on many occasions, notably by Roy and Graham Brown²⁸, who were amongst the first workers to recognise the control of the circulation exercised by capillaries. Of recent years a noticeable trend of physiological opinion has been the tendency to reject the view that active vasodilatation is controlled by the central nervous system and to refer such vasodilatation to a peripheral and locally acting stimulus. Thus Markwalder and Starling²² have concluded that vasodilatation of the coronary vessels may be brought about by the collection of metabolites in the muscle; Barcroft and Piper² and Barcroft and Kato³ have expressed similar views in regard to vasodilatation in the case of the submaxillary gland, be it awakened originally by nerve stimulation or otherwise, and in regard to the flow to voluntary muscle. Likewise Anrep¹ suggests the accumulation of asphyxial products as the cause of the hyperæmia which follows the release of an occluded circulation. The idea is no new one when applied to injury. For nearly a century tentative views have been expressed suggesting that toxic substances are liberated by burns; it is, however, in the war period especially that we find evidence first beginning to accumulate in an impressive way. Observations and suggestions relating to tissue injury and its effects have been reviewed so recently and so fully that it becomes redundant to discuss them at length; we may draw attention particularly to the general statements of Ebbecke¹⁶, Bayliss⁶, Krogh¹⁸ and Dale¹¹. In the present discussion it is most suitable to summarise those observations and conclusions which seem relevant to our own work, and to attempt to place these in perspective with each other. We do so in the succeeding paragraphs.

Reactions to the type poison histamine. When introduced in minute doses into the skin this poison produces a characteristic series of independent phenomena comprising (a) local dilatation of the minute blood vessels, capillaries, venules and terminal arterioles, by direct action, (b) a widespread

dilatation of neighbouring arterioles through the medium of a local reflex mechanism and (c) increased permeability of the vessel walls by direct action. This series of phenomena may be termed as a whole the type reaction, it leads to manifest œdema of the true skin. When histamine finds its way into the general circulation it produces, as Dale, Laidlaw and Richards^{14 & 15} have demonstrated, a general dilatation of the bed of minute vessels beyond the main arterioles, and an increased permeability of the walls of the minute blood vessels. These effects lead, when sufficient poison is introduced, to an impounding of blood in the capillary reservoir accompanied by serious loss of blood fluids into the tissue spaces; owing to this diversion of the blood the central vessels are depleted, a profound and lasting fall of blood pressure follows, leading to a condition of collapse to which the term "histamine shock" has been applied. The likeness between this state and anaphylactic shock on the one hand, between it and wound shock on the other, has been emphasised by Dale and Laidlaw^{12 13 & 14} at various times.

Reactions to injury. When a firm stroke is laid down on a sensitive skin, when the normal skin is repeatedly stroked in the same fashion or suffers a single and more severe injury of a similar kind, the type reaction follows, is displayed in all its details and leads to œdema of the true skin. A similar reaction though less intense follows a simple pin prick or a scratch. These reactions to injury are ascribed on independent evidence to the liberation of a diffusible substance in the skin having a histamine-like action on the minute blood vessels and nerves of the skin.

During the period of the war evidence accumulated which strongly suggested that the condition termed secondary wound shock results when the products of bruising and laceration of skin and deeper tissues are absorbed into the general circulation. The strongest single piece of evidence for this view is perhaps the demonstration that secondary shock does not develop when the channels of absorption from the damaged tissues are closed (Bayliss⁶, Cannon¹⁰ and others²⁶). In severe secondary wound shock it has been shown that there is a profound and prolonged fall of blood pressure, that much of the blood has left the main vessels, that it is concentrated by the loss of its fluids into the tissue spaces, and that the volume of blood in circulation is much decreased²³, the resemblance to histamine shock being thus demonstrated as remarkably close. Lastly, substances having a depressor effect on blood pressure have been recovered from many tissues of the body, and histamine itself has in one instance been isolated, namely, from the mucous membrane of the bowel⁵.

Reactions to scalds and burns. A mild scald of the skin is followed by the type reaction, and leads to œdema of the true skin and ultimately to blistering of the skin. These reactions are likewise attributed to the liberation in the skin of a diffusible substance having a histamine-like action on the minute vessels and nerves of the skin.

More extensive burns give rise to a secondary shock-like condition, and this has been suspected for very many years to result from the absorption of toxic substances; full references to this subject will be found in the articles of Bardeen and of Robertson and Boyd^{16, 27}. Substances have been recovered from burnt skin which, when introduced into a healthy animal, induce a condition resembling shock²⁷.

It is difficult to review a series of observations such as are contained in the last few paragraphs without being impressed by the manner in which they are in process of fitting themselves together into a co-ordinate and simplified whole.

From the simple reactions of a healthy skin to the relatively mild stimuli such as are experienced daily by almost all; through the more serious, though still trivial local injuries, the bruise, the blister and the small scald, which find their simple household remedies; to the most grave mechanical injuries and extensive burns, which in their late manifestations endanger life, we pass by transition. It begins to be apparent why this transition is throughout a transition of quantity and not of quality; for, underlying the whole series of reactions there is seemingly one chief determining cause, the unvarying reply of the affected cell to injury; this response of the cell, protective as it is to the cell itself, when united with that of neighbours, produces a massive action, threatening or terminating the life of the organism as a whole; an example which is not the sole example of conflict between the cell and the community of which it is a member.

CONCLUSIONS.

1. When a solution of histamine is punctured into the skin it gives rise to a local response comprising three independent reactions, namely, (a) a local dilatation of the capillaries, venules and arterioles by direct action, (b) a widespread dilatation of surrounding arterioles, resulting from a local reflex, and (c) a locally increased permeability of the walls of minute blood vessels by direct action. This total reaction is termed the type reaction and leads to local oedema of the skin.

2. The vascular reactions of the skin in urticaria facticia in response to single strokes, and incidentally of normal skins to repeated strokes, are closely compared. The reactions are in general and in detail identical with those of the type reaction.

3. From this comparison, and from further evidence of a more direct kind, it seems clear that the reactions of the skin to stroking result from the liberation of a chemical substance in the skin, this substance having a histamine-like action on the blood vessels and nerves.

4. Less extensive comparisons of the skin's responses to scratches and pin pricks, and to excessive heat, indicate that these responses are of a similar or identical kind and that these are determined by a chemical stimulus.

5. These observations are discussed and brought into perspective with shock arising from histamine, from severe mechanical injuries and from severe burns, as these have been described by previous workers.

6. The increased permeability of the skin vessels, consequent upon a histamine or mechanical stimulus locally applied, is shown to be shortly followed by a peculiar condition of partial or complete refractoriness to further stimulation of the same kinds: as this condition of refractoriness becomes established, increased permeability disappears. The meaning of this phenomenon is discussed at length.

To our colleagues, Dr. A. M. H. Gray and Dr. J. W. McNee, we are much indebted for several cases of urticaria factitia which they have kindly placed at our disposal; we are equally indebted to Dr. Picton Phillips for the opportunity of examining cases of old-standing sensory nerve lesions under his care.

Note on the response of the guinea pig's uterus. Much time and labour has been spent in testing the effects of wheal fluid upon the tone of short pieces of the guinea pig's uterus. The fluid has been obtained from small burns of our own arms, and from the prominent stroke wheals of *Subject I*, in doses up to 1 or 2 cubic millimetres. For this purpose a variety of different methods has been employed; these we do not propose to discuss, other than to state that the uterus is suspended in a very small bath through which a stream of oxygenated Ringer-Locke solution passes. The wheal fluids constantly produce tonic contraction of the uterus, the curves being identical in form with those yielded by histamine. We estimate the dilution of the toxic substance in the wheal fluids, in terms of histamine base, at approximately 1 in 1,500,000. This estimate is consistent with others already discussed in our paper. The difficulty of the work lies in the minute doses of fluid available, and we are unable to introduce our results into the main body of our paper, because our controls have failed us. As yet, a method has not been obtained in which, while wheal fluid yields contractions, plasma obtained from the same subjects, and similarly treated and in similar doses, gives constantly smaller contractions or no contraction. From time to time the contrast between plasma and wheal fluid has seemed sufficient, but on more numerous occasions the effects of the two fluids have seemed to be identical.

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OBSERVATIONS RELATING TO THE NERVE SUPPLY OF THE CORONARY ARTERIES OF THE TORTOISE.*

PART II.—PERFUSION OF THE ARTERY.

By A. N. DRURY and J. J. SUMBAL (Bratislava).

(From the Cardiac Department, University College Hospital Medical School.)

IN a previous paper the effects of locally applying adrenalin, and of stimulating the vagus upon the coronary artery have been described⁵. In these experiments changes in calibre were determined by viewing the arteries directly through a microscope in the naturally beating heart with intact circulation. This method, in spite of its manifold advantages, is limited by the fact that only very definite changes in the calibre of the vessels can be determined with any degree of certainty. For instance, although vagal stimulation produced no visible change in the normal artery, it definitely dilated a vessel which had been previously constricted by the local application of adrenalin. In order, therefore, to elicit any small change in vessel calibre which may result from nerve stimulation, and which cannot be appreciated by direct observation, and to substantiate further the previous and more subjective findings, the question has been re-examined by perfusing the whole coronary system. The influences of vagal stimulation and adrenalin have been reobserved, and the effects of sympathetic and coronary nerve stimulation have also been investigated, the reaction of the coronary vessels being determined by the change in the amount of perfusion fluid flowing into the coronary system.

Method.

As in the previous experiments, the tortoise (*Testudo graeca*) has been used.† The animal is pithed and tied firmly by its four limbs to a board, shaped to receive the rounded dorsal carapace. The anterior third of the ventral carapace is removed, great care being taken to avoid damage to the veins lying close beneath, since when a vein is damaged air immediately enters it and, finding its way to the heart, may be forced into the coronary system, thus rendering the experiment useless. The pectoral girdle is cut through, and the two forelimbs dissected and pulled away so that the pericardium

* Observations undertaken on behalf of the Medical Research Council.

† The experiments were performed during the autumn and winter.

and the basal vessels are exposed. The pericardium is opened and the heart and the vessels laid bare. Stitches are then placed in the pericardial attachments of these basal vessels and fixed so that the right side of the aorta can be easily reached. The coronary artery of the tortoise springs as a single vessel* fairly high up on the right side of the aorta, and divides quickly into two branches. The original single stem is variable in length and calibre in different tortoises, but in the great majority it is sufficiently large and long enough to allow a small glass cannula to be introduced and tied in. A thin stitch having been passed in and out of the aorta so as to encircle the coronary artery close to its origin, the cannula is introduced into the aorta through a small cut about 5 mm. above the origin of the coronary artery and is passed into the artery and tied off, a second ligature being tied subsequently around the cannula. The amount of fluid flowing through the coronary vessels is measured by means of Edgar-Atzler and Frank's method⁶, which allows variations in inflow to be determined from moment to moment. The perfusion fluid is held in a container of large cross section so that the passage of a considerable amount of fluid does not materially change the level of the perfusion fluid, which is placed at a height above the level of the heart giving a usual pressure of 30-40 cms. H_2O . Alterations in the level of the perfusion fluid have a considerable influence upon the rate of inflow, pressures of 60, 50, 40, 30 and 20 cms. H_2O being associated with inflows of 4.0, 3.4, 1.9, 1.1 and 0.36 ccs. per minute respectively, with a constant cardiac rate. Ringer's solution is perfused, the composition being either that given by Daly and Clark² or Demoor³, and no difference in the results is occasioned by such slight alteration in its composition. The heart was observed throughout the experiment, and œdema noted only on the few occasions when the heart had been perfused for many hours. To avoid this effect, 3.5 per cent. gum acacia was added to the perfusion fluid in a few experiments without affecting the general findings. Any hindrance to the outflow through the coronary vein is prevented by cutting open the auricle or the sinus venosus. Thin threads are tied to the auricle and ventricle and attached to light levers, which record the respective systoles on a smoked drum. The perfection of these records is sacrificed to a more important consideration, namely, the most advantageous adjustment of the heart's position to keep the coronary artery and vein free from kinks or any possible obstruction. They afford, however, a sufficient index of variations in the strength of the auricular and ventricular systoles, record the cardiac rate and signal by shifting the zero of the curves, any movement of the heart's position which may occur during the experiment.† The inflow

* On one or two occasions two small coronary arteries have been found arising from the aorta, one on the anterior aspect, the other on the right and somewhat posterior aspect.

† Any movement of the lie of the heart during stimulation by altering the position of the cannula in the coronary artery is liable to give rise to an altered inflow. As the position originally chosen is always that which gives the greatest inflow, retardation is usually produced by movement.

is written upon the same drum, each drop of a lever representing the passage of a certain volume of perfusion fluid into the artery; the number of drops of the lever made by the passage of 1 cc. of perfusate through the cannula being determined at the end of the experiment. When the effect of vagal stimulation is being investigated, the anterior third of the ventral carapace is removed, the vagus exposed in the neck and there stimulated. The stimulation of the sympathetic nerve requires removal not only of the whole ventral carapace but also a piece of the dorsal carapace on the side on which the stimulated sympathetic lies, since it is necessary to dissect out the sympathetic ganglia, the lung being carefully withdrawn. These ganglia lie as a chain close to the subclavian and vertebral vessels^{4 & 9} and are easily exposed in this manner; usually three ganglia are present, but either two or all may be fused. The cardiac nerves are sent off from the middle ganglion or (if they are all united) from the upper end of that mass. The middle sympathetic ganglion has been stimulated. The stimulation of the coronary nerve is effected by lifting up the heart sufficiently to allow a stimulator to be placed upon the nerve which runs alongside the coronary vein. These electrodes must be fixed permanently because, if they alter in position, they may press upon the coronary vein and mechanically change the inflow. As large a cannula as possible is usually introduced and passed up the vein from the sinus venosus and clamped in position; the stimulator could then be placed upon this cannula and the nerve stimulated with much less risk of mechanical disturbance. The cardiac rate is maintained throughout the experiment by means of break shocks applied to the ventricle at a constant rate slightly above that of the normal heart rate. The influence of change of rate upon the inflow into the coronary system is inconsiderable. Ventricular rates of 14, 17, 23, 31, 39 (the last being associated with 2:1 response of the auricle) per minute have yielded inflows of 1.8, 1.8, 1.85, 1.9 and 1.7 cc. per minute respectively with a constant perfusion pressure. In the tables of the coronary inflow the amount of inflow in cc. for each successive minute has been calculated. This method of tabulation, while obviating errors arising from slight alterations in flow from moment to moment, tends to mask the evanescent effects produced by nerve stimulation since an average and not a maximal effect is tabulated.

The effect of sympathetic stimulation.

The influence of stimulating the sympathetic ganglia has been tested in five tortoises (see Table I). The coronary inflow either remains unchanged upon stimulating the ganglia on the right or the left side, or is decreased.* The extent of the decrease varies in different tortoises, and in the most striking examples amounts to about 50 per cent., while, on the average, it is

* The path of the sympathetic fibres supplying the coronary vessels is unknown; should these join the coronary artery close to its origin they may be caught up by the ligature holding the perfusion cannula and damaged, and thus negative results obtained.

reduced about 30 per cent. Fig. 1 shows a record of such an effect, the ventricle being driven rhythmically throughout at a rate of 38 per minute. At the beginning of the record the inflow is about 0.78 cc. per minute. The middle cervical ganglion⁹ is then stimulated on the right side, and after a short delay the rate of flow is seen to decrease and amounts to 0.51 cc. per minute. After withdrawing stimulation the inflow increases again and at the end of the record amounts to 0.78 cc. per minute. The auricle shows a slightly increased force of contraction during the stimulation; no change is seen in the ventricular contractions. The influence of similar stimulation upon the same heart beating naturally produced a rise in cardiac rate from 18 per minute to 26 per minute. In our experiments sympathetic stimulation has not produced the great augmentation in auricular systole and of cardiac rate, spoken of by Gaskell⁹. On a few occasions, when the heart has been beating naturally at a low rate of 8-12 per minute, considerable

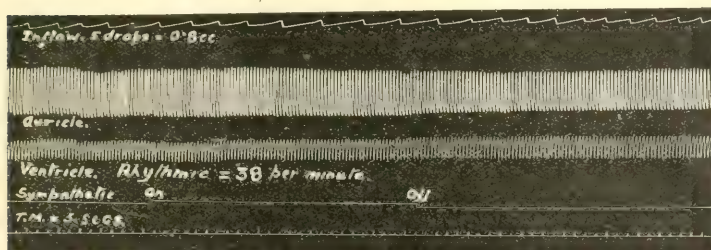


Fig. 1. (·5, 8). Tortoise J. Effect of stimulation of sympathetic upon coronary inflow. Perfusion pressure = 40 cms. H_2O . Time marker = 5 secs.

augmentation has been noted in both the cardiac rate and in the force of auricular systole upon sympathetic stimulation; but after the heart has been driven rhythmically for some time the auricular systole appears to be little affected. On all occasions when the coronary flow has been decreased, either an augmentation of some degree has been seen, or a 2 : 1 response of the auricle to the ventricle driven at a relatively high rhythmic rate has been converted to a 1 : 1 response. There appears to be no constant quantitative relation between the sympathetic action upon the force of auricular systole and change in the inflow, some of the greatest changes in the latter being associated with little change in auricular systole. In agreement with Gaskell⁹ we have noted no change in the ventricular systole during sympathetic stimulation.

The influence of adrenalin chloride.

Parke Davis's adrenalin chloride has been used, and the 1 in 1,000 B. P. solution diluted with Ringer's solution. In some experiments two perfusion bottles were connected with the same recording apparatus, one containing Ringer's solution, the other a solution of adrenalin chloride of a dilution of 1 in 1,000,000, or 1 in 500,000 with Ringer's solution, so that either solution could be perfused at will without change in the perfusion pressure. Perfusion of the coronary vessels for a few minutes with such dilute solutions always gives rise to a great retardation of the coronary inflow, which only returns to its original rate after some hours of further perfusion with Ringer's solution. In the majority of experiments, therefore, a small amount of a dilute solution of adrenalin has been slowly injected into the rubber tubing carrying the perfusion fluid; a method which allows more transient effects to be witnessed. A retardation of the inflow has always occurred, and injections of 0.2 cc. of a 1 in 10,000 solution, usually stop the inflow almost entirely. The reaction with such solutions is long lasting, passing off in about one hour. The ventricle, driven rhythmically throughout the experiments, shows no augmentation in systole; while the auricular systole is always increased slightly, though not in a degree comparable to that seen by Elliott⁷. We are inclined to consider that the divergence of this finding from that of previous workers to be due to the use of a rhythmically driven heart in our experiments. The natural cardiac rate has occasionally been increased by the injections, but usually not sufficiently to disturb the rhythmic rate. Fig. 2 is a record from an experiment in which 0.2 cc. of adrenalin chloride (1 in 100,000) has been injected slowly into the perfusion tubing. At the beginning of the record the inflow is shown to amount to 0.72 cc. per minute; after being momentarily disturbed by the injection, it is soon seen to be decreased, amounting to only 0.08 cc. per minute. Eighteen minutes later the rate of inflow is seen to be 0.30 cc. per minute, the original rate not being restored for 45 minutes. In this experiment the ventricle was driven rhythmically throughout, and at the end of the record the natural cardiac rate was sufficiently accelerated to disturb the rhythmic beats: the ventricular systoles are seen to be unchanged throughout. The auricle follows the ventricle throughout, and its force of contraction is slightly augmented. Adrenalin has been injected in very many tortoises; examples showing the degree to which inflow is retarded by such injections are given in Table II.

In the mammal, as Dale¹ has shown, it is possible to convert the vasoconstrictor action of adrenalin on peripheral vessels into one of dilatation by a preliminary injection of ergotoxin. It is suggested by this observer that both vasoconstrictor and vasodilatator fibres exist in the mammalian sympathetic system, but that the vasoconstrictor fibres predominate and normally mask the vasodilatator action. If ergotoxin is given, however,

TABLE II.
Influence of adrenalin chloride upon coronary inflow. Inflow in cc. per minute for successive minutes.

Tortoise	E.	E. contd.	A.	B.	B. contd.	M.
Perfusion pressure in cms. H ₂ O	30		40	30		40
Rhythmic stim. per minute	20					40	38		24
0-62	0-62				0-48	0-72	1-8	1-0	0-70
0-58	0-47				0-47	0-72	1-5	1-0	0-72
0-62	0-47					0-72	1-5	1-0	0-70
Adrenalin				Adrenalin	Adrenalin	Adrenalin	Adrenalin	Adrenalin	Adrenalin
1 in 1,000,000				1 in 500,000	1 in 500,000	0-3 cc.	0-2 cc.	0-2 cc.	0-2 cc.
perfused				perfused		1 in 100,000	1 in 10,000	1 in 10,000	1 in 100,000
0-32	0-41			0-41		0-57	1-5	1-0	0-56
0-43	0-36			0-36		0-72	1-1	0-8	0-44
0-39	0-31			0-31		0-65	1-0	0-5	0-28
0-39	0-34			0-34		0-50	0-8	0-5	0-16
0-52	0-29			0-29		0-43	0-9	0-4	0-12
10 minutes	0-26			0-26		0-57	0-8	20 minutes	0-08
elapse	0-23			0-23		0-50	0-8	elapse	0-06
0-42	0-15			0-15		0-43	0-8	0-50	10 minutes
Ringer	0-11			0-11		0-57	0-5	10 minutes	elapse
perfused	Ringer			Ringer		0-50	0-5	elapse	0-30
0-43	perfused			perfused		0-50	24 minutes	0-80	0-30
0-44	0-08			0-08		0-57	elapse	5 minutes	0-36
0-44	0-04			0-04		0-54	0-8	elapse	0-36
0-43	0-01			0-01		0-54	0-8	1-0	0-38
0-44	0-01			0-01		0-43	0-7	1-0	23 minutes
0-41	0-01			0-01		0-39	1-0	1-0	elapse
0-41	10 minutes			10 minutes		0-47	1-3		0-70
0-40	elapse			elapse		10 minutes	1-0		0-68
0-42	0-10			0-10		0-39	1-3		0-70
						0-39	1-4		

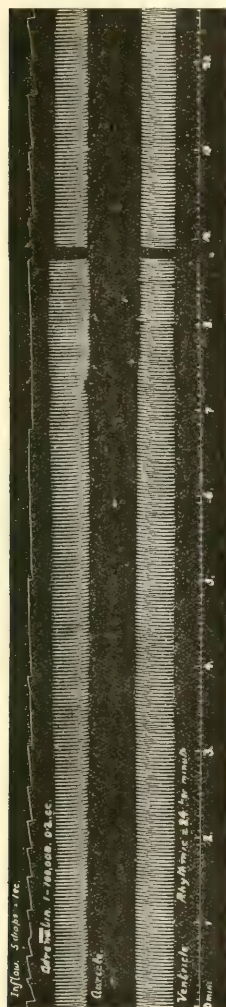


Fig. 2 (·7.17). Tortoise M. Effect upon coronary inflow of introduction of 0.2 cc. of a 1 in 100,000 solution of adrenalin into the perfusion fluid. Perfusion pressure=40 cms. H_2O . Time marker—5 secs.

the vasoconstrictor mechanism is supposedly stimulated, leaving the vasodilator mechanism untouched, and a subsequent dose of adrenalin acting upon this mechanism dilates the vessel. In five tortoises adrenalin has been introduced during the perfusion of a solution of ergotoxin. The strength of the ergotoxin solution used was either 1 in 200,000, 100,000 or 50,000. In one tortoise (Tortoise L, Table III) a small increase of flow was obtained upon injecting adrenalin, but the remaining animals gave the usual decreased flow. The ergotoxin itself, as in the mammal, in all cases retarded the inflow, in some instances very considerably, showing the dose to be effective; despite this action, no subsequent vasodilatation was constantly produced by adrenalin. Thus, in the tortoise clear evidence for sympathetic vasoconstrictors is alone forthcoming.

The influence of vagal stimulation.

The vagus nerve has been stimulated in a large number of tortoises. The reaction is usually an increase in coronary inflow; in some, however, no

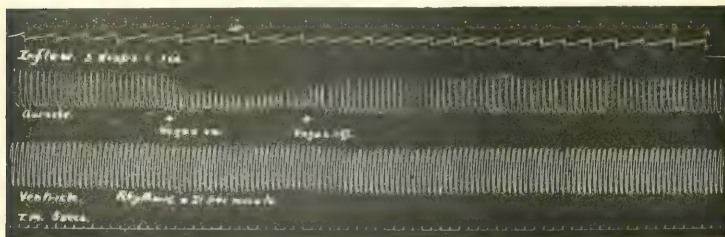


Fig. 3 ($\times 5$ 11). Tortoise S. Effect of stimulation of right vagus nerve upon coronary inflow. Perfusion pressure = 40 cms. H_2O . Time marker = 5 secs.

change is to be observed. Both vagi have been tested, being stimulated in the neck with sufficient current strength to produce a profound auricular effect. The increase in flow usually amounts to about 30 per cent., but on some occasions may rise to 50 per cent. or more. The effect does not usually appear immediately after stimulation, but is delayed so that the full reaction is not seen until two or more minutes have elapsed and, if the stimulation has been short, often occurs as the auricular effect is passing off. After withdrawing the stimulation the increased inflow on some occasions persists and a second stimulation opens up the vessels still further, so that the coronary inflow can be increased by a series of steps: on other occasions the rate of inflow prior to stimulation is soon re-established. No parallelism appears to exist between the vagal influence upon the auricle and the degree

TABLE IV.
Influence of vagal stimulation upon coronary inflow (normal vessels). Inflow in cc. per minute for successive minutes.

[illegible]

of increased flow. Fig. 3 is an illustration. At the beginning, the inflow is at a rate of 0.64 cc. per minute; the vagus is then stimulated and after a short delay the inflow is seen to be increased, reaching 1.20 cc. per minute at the end of stimulation, and slowly decreasing again as the influence of stimulation passes off; the prestimulation rate of inflow is restored in 7 minutes. The ventricle, being rhythmically driven, shows no change in either the rate or force of its contractions. The auricle is slowed owing to the development of A-V block and its contractions are considerably weakened. The observations on vagal stimulation are further illustrated by Table IV.

The influence of vagal stimulation upon vessels constricted by adrenalin. In a few tortoises the influence of vagal stimulation upon adrenalinised vessels has been tested (Table V). The vessels have been constricted by introducing a suitable dose of adrenalin and the right or left vagus nerve

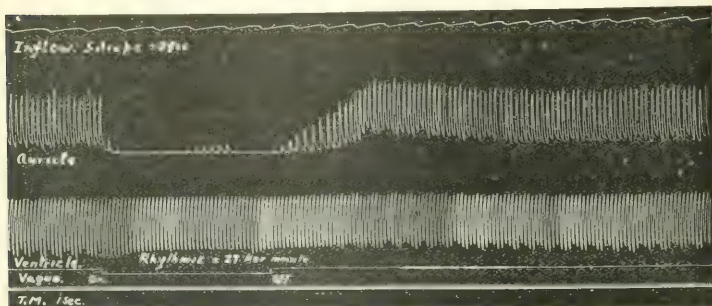


Fig. 4 ($\times \frac{1}{2}$). Tortoise E. Effect of stimulation of left vagus nerve upon coronary inflow, vessels constricted by adrenalin. Perfusion pressure = 45 cms. H_2O . Time marker = 1 sec.

subsequently stimulated. On some occasions, if this stimulation occurs very soon after the vessels are constricted, no effect is produced, but if a sufficient interval elapses after introducing adrenalin, the inflow is always increased. Upon withdrawing stimulation, the inflow rate on some occasions returns to that present prior to stimulation: it can then be again increased by re-stimulating the vagus nerve: on other occasions the increased rate of flow persists and the vessels can be opened up more widely by a series of successive stimulations though the pre adrenalin rate is not always fully attained. In Fig. 4 prior to vagal stimulation the inflow is seen to amount to 0.39 cc. per minute (before the introduction of adrenalin it amounted to 0.80 cc. per minute). The left vagus is stimulated and the inflow after a short delay is increased to 0.52 cc. per minute. The pre-stimulation inflow is slowly re-established after withdrawing stimulation. In this

The influence of vagal stimulation upon coronary inflow. Vessels constricted by adrenalin. Inflow in ccs. per minute for successive minutes.

Tortoise	C.	D.	E.	E. contd.	E. contd.	H.	I.	I. contd.
Perfusion pressure in cms. H ₂ O ...	40	45	47			27	30	
Rhythmic stim. per minute ...	21	18	27			27	26	
	0.08	0.03	0.30	0.39	R. vagus stim.	0.24	0.16	0.84
	0.08	R. vagus stim.	0.30	R. vagus stim.	0.37	0.24	0.20	0.84
	0.08	0.04	R. vagus stim.	0.45	0.39	R. vagus stim.	0.16	0.84
	0.08	0.06	0.50	0.50	0.42	0.29	0.20	R. vagus stim.
	0.19	0.06	0.65	0.45	Stim. off	0.36	0.20	0.90
	0.19	0.06	Stim. off	0.41	0.42	0.40	0.20	0.90
	0.19	Stim. off	0.52	0.39	0.44	Stim. off	0.20	Stim. off
	0.22	0.07	0.39	0.36	0.42	0.40	0.24	1.04
	0.22	0.04	0.48	0.36	0.49	0.44	0.24	Reconstructed by adrenalin
	Stim. off	0.02	0.52	0.31	L. vagus stim.	L. vagus stim.	0.24	0.56
	0.25	0.04	0.45	0.35	0.04	0.46	R. vagus stim.	0.56
	0.25	0.05	L. vagus stim.	R. vagus stim.	0.04	0.52	0.24	R. vagus stim.
	0.27	0.04	0.63	0.62	0.58	0.52	0.28	0.52
	0.24	R. vagus stim.	0.47	0.90	Stim. off	Stim. off	0.30	0.60
	0.21	0.05	0.43	Stim. off	0.54	0.54	0.34	0.64
	0.18	0.04	Stim. off	0.98	0.60	0.60	Stim. off	Stim. off
	R. vagus stim.	0.04	0.39	1.00	0.60	0.60	0.36	0.70
	0.21	Stim. off	0.39	1.00	0.48	0.62	0.38	0.70
	0.24	0.07	R. vagus stim.	1.00	0.45	R. vagus stim.	R. vagus stim.	0.70
	0.26	0.07	0.45	Reconstructed by adrenalin	R. vagus stim.	0.67	0.44	R. vagus stim.
	0.29	9 mins. elapse	0.45	0.09	0.55	0.60	0.44	0.80
	Stim. off	0.10	Stim. off	0.09	0.65	0.60	Stim. off	0.90
	0.32	0.10	0.39	0.15	0.65	0.60	0.48	0.92
	0.28	L. vagus stim.	0.34	R. vagus stim.	Stim. off	Stim. off	0.50	1.00
	0.32	0.11	0.39	0.15	0.52	0.60	0.60	0.94
		0.13	0.34	0.21	0.52	0.60	0.60	0.80
		0.13	L. vagus stim.	0.23	0.57		L. vagus stim.	1.00
		0.13	0.50	Stim. off			0.62	
		Stim. off	0.52	0.26			0.72	
		0.15	0.52	0.23			0.80	
		0.14	Stim. off	0.26			Stim. off	
		0.11	0.50	0.31			0.80	
		0.11	0.41					

observation the ventricle was responding to rhythmic shocks at 27 per minute throughout, and the completeness of the vagal stimulation is reflected in the auricular record.

TABLE VI.

Influence of atropine upon coronary inflow. Inflow in ccs. per min. for successive minutes.

Tortoise	O.	P.	R.
Perfusion pressure in cms. H ₂ O	40	40	40
Rhythmic stim. per min.	14	28	18
	0.64	0.96	1.76
	0.64	0.96	1.66
	0.62	0.96	1.70
Atropine	Atropine	Atropine	
0.1 mg.	0.15 mg.	0.1 mg.	
0.62	0.86	1.40	
0.58	0.76	1.56	
0.56	0.76	1.56	
0.50	0.76	1.46	
0.54	0.74	1.32	
0.54	0.76	1.32	

The influence of atropine sulphate. If atropine sulphate is added to the perfusate the coronary inflow is decreased. This action of atropine is consistent with a loss of vagal tone, since vagal stimulation produces dilatation. If the vagus nerve is stimulated after complete atropinisation, no change in the coronary inflow is produced, either in the normal vessel or in the vessels constricted by adrenalin. This failure to react after atropine has been observed in tortoises in which vagal stimulation has previously been especially effective in opening up both normal vessels and those constricted by adrenalin; after the influence of the atropine has passed off, the usual reaction to stimulation, namely, dilatation, is restored again. The constrictor effect of sympathetic stimulation is unaffected by complete atropinisation.

The coronary nerve.

The only known effects of coronary nerve stimulation are those originally reported by Gaskell¹⁸; they are central effects, the heart rate being slowed and the systoles of the auricle being conspicuously weakened. But the coronary nerve sends branches in a peripheral direction, and these course on the ventricle. The function of these fibres has not been explored previously. Stimulation of the coronary nerve in its length may either increase or decrease the rate of flow through the coronary vessels, and this dual effect has been found not only in different animals but in one and the same animal. Owing to the close proximity of coronary nerve and vein it is

impracticable to stimulate the one without risk of current escaping to the other. It was thought that the retarded flow sometimes seen might be occasioned by escape current stimulating the wall of the vein and changing its calibre, an effect which would reduce the outflow from the coronary vessels and raise the resistance in them. Various procedures have been adopted to ensure free outflow from the veins, such as introducing a cannula into the vein, slitting up the vein or puncturing the collecting veins as these encircle the base of the ventricle, but the retardation of flow when it occurs cannot be abolished by any of these methods. It would appear, therefore, that both the increased and decreased flow are to be attributed to nerve stimulation. Whether the inflow is decreased or augmented, the auricular systoles are weakened. In Fig. 5 is an illustration of the inflow being

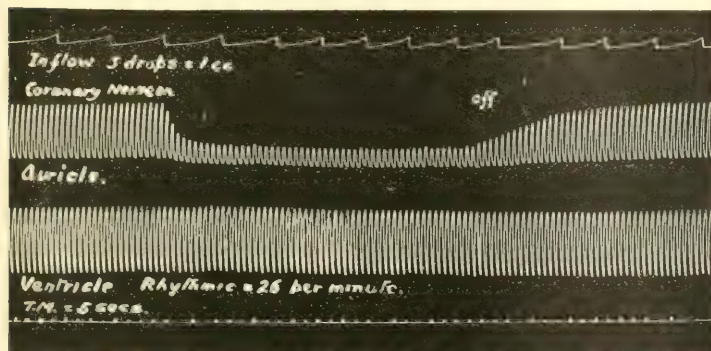


Fig. 5 ($\times 57$). Tortoise X. Effect of stimulation of coronary nerve upon coronary inflow. Perfusion pressure = 30 cms. H_2O . Time marker = 5 secs.

increased from 0.56 cc. per minute to 0.68 cc. per minute as a result of coronary nerve stimulation. The ventricle responding to rhythmic shocks remains unchanged, the auricular systoles being considerably weakened during the period of stimulation. If the central end of the nerve is cut and the peripheral portion stimulated, the changes in the inflow are the same as those before section, though the auricular systole now remains unaltered in strength. In two tortoises the vessels were constricted by adrenalin; in one, the inflow which before giving adrenalin was always decreased by nerve stimulation, was similarly affected after the adrenalin was administered. In the other, the inflow was both increased and decreased by stimulation before, but after giving adrenalin was constantly increased. This second observation suggests that the decrease in flow originally seen resulted

TABLE VII.

Influence of stimulation of coronary nerve upon coronary inflow. Inflow in ccs. per minute for successive minutes.

Tortoise	W.	W. contd.	N.	AB.	BB.	CB.	EB.	PB.	FB contd.	DB.
Perfusion pressure in cns. H ₂ O	30		40	45	45	40	45	45		40
Rhythmic stim. per minute	24		26	25	22	29	22	18		15
	0-32	Nerve cut.			1-04	0-94	1-16	0-62	0-84	0-40	0-44	0-54
	0-32	peripheral			1-12	0-88	1-16	0-60	0-84	0-38	0-44	0-54
	stim. on	portion			1-14	0-88	stim. on	stim. on	stim. on	0-40	0-40	0-54
	0-30	stimulated			1-04	stim. on	1-10	0-54	0-90	0-38	Nerve cut.	stim. on
	0-24	0-32			1-18	0-96	0-80	0-48	0-90	stim. on	peripheral	0-50
	0-36	0-32			stim. on	0-94	stim. off	stim. off	stim. off	0-46	portion	0-38
	0-36	0-32			1-26	stim. off	0-84	0-64	0-80	0-46	stimulated	stim. off
	0-36	stim. on			1-20	0-86	1-06	0-60	stim. on	stim. off	0-40	0-48
	stim. off	0-32			stim. off	0-92	1-20	stim. on	0-84	0-40	stim. on	0-46
	0-24	0-36			1-10	0-92	stim. on	0-40	0-76	0-40	stim. on	0-50
	0-20	0-36			1-12	0-84	1-14	0-46	0-72	0-40	0-48	
	stim. on	0-40			1-16	stim. on	0-96	stim. off	stim. off	0-40	0-40	
	0-24	stim. on			Pressure	0-86	stim. off	0-52	0-60	0-36	stim. off	
	0-32	0-32			changed	0-88	0-88	0-52	0-78	0-40	0-40	
	0-36	0-32			to 30 cms.	stim. on	1-12	0-60	stim. on	0-44	0-40	
	0-40				0-56	0-90	1-32		0-80	stim. on	0-40	
	stim. off				0-62	0-88	1-36		0-84	0-44	0-40	
	0-32				0-64	0-88	1-30		0-80	0-48	stim. on	
	0-32				stim. on	stim. on	1-24		stim. off	0-36	0-48	
	0-30				0-70	0-84	1-24		0-76	stim. off	0-48	
	0-24				0-64	0-78	stim. on		0-76	stim. on	0-40	
	0-26				stim. off	stim. off	1-08			0-32	0-40	
	stim. on				0-78	0-78	0-86			0-38	0-40	
	0-30				0-84	0-88	stim. off			0-40	0-40	
	0-26				0-80	0-88	0-88			stim. on		
	0-30				0-86		1-10			0-54		
	0-36				stim. on		1-20			0-48		
	0-38				0-92		1-34			0-48		
	stim. off				0-94		1-46			stim. off		
	0-32				stim. off		1-40			0-48		
					0-88							
					0-84							

from sympathetic stimulation, and that this effect had been abolished or reduced by adrenalin. In four tortoises sufficient atropine was given completely to paralyse the vagal nerve endings: in two of these prior to atropinisation, the inflow had been constantly decreased by stimulating the coronary nerve, and the same result was seen after atropinisation. In the other two, before atropinisation stimulation frequently increased the inflow; this effect was completely abolished by atropine. It would appear that stimulation of the coronary nerve, which contains fibres coursing peripherally gives rise either to vasodilatation or vasoconstriction. The vasodilator effect is abolished by atropine and is evidently vagal. With regard to the vasoconstrictor effect, which sometimes appears, its meaning is not entirely clear: it is either attributable to stimulation of sympathetic fibres in the coronary nerve itself or of neighbouring nerve fibres of the same kind in the vicinity.

SUMMARY.

The conclusions recorded by Drury and Smith⁵, namely, that adrenalin constricts the coronary arteries, and that vagal stimulation dilates the vessels when so constricted, have been fully borne out by the observations upon the perfused coronary system, detailed in this paper. It is now shown that stimulation of either the right or left vagus nerve dilates the normal coronary vessels as well as those previously constricted by adrenalin, while stimulation of the sympathetic nerve constricts the vessels. Ergotoxin, in a dose sufficient to produce a definite constriction of the vessels fails to unmask any dilator action of adrenalin; the evidence so far derived from nerve stimulation and adrenalin injections in the tortoise supports vasoconstrictor sympathetic effects only. Atropine, in doses sufficient to paralyse completely the vagal nerve endings, immediately gives rise to a slight constriction of the vessels; this effect is attributed to removal of vagal tone. Atropine abolishes the dilator effect of vagal stimulation and leaves the constrictor effect of sympathetic stimulation unaffected. Stimulation of the coronary nerve both dilates and constricts the vessels, at the same time weakening the auricular systole. After complete atropinisation constriction of the vessels is alone seen. The coronary nerve is demonstrated to contain vasodilator fibres belonging to the vagal system and running peripherally to the ventricle; it possibly contains constrictor sympathetic fibres coursing peripherally, though this remains unproved.

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THE ACTION OF PITUITARY EXTRACTS, ACETYL-CHOLINE AND HISTAMINE UPON THE CORONARY ARTERIES OF THE TORTOISE.*

By J. J. SUMBAL (BRATISLAVA).

(From the Cardiac Department, University College Hospital Medical School.)

THE effects of vagal and sympathetic nerve stimulation upon the coronary vessels of the tortoise have already been reported^{11, 12}, and these show clearly that the reactions of these vessels to such stimulation are not comparable to those usually described as occurring in the mammalian heart. While most observers report that vasodilatation follows sympathetic, and that vasoconstriction follows vagal nerve stimulation in the mammal, the reverse effects are uniformly seen in the tortoise, whether the reaction be judged by microscopic observations of the vessels or by changes in the flow of a perfusion fluid into the main artery. Therefore it seemed desirable to test the effect of certain substances, the effects of which upon the vascular system in other animals are already known, namely, pituitary extract, acetyl-choline and histamine. *Testudo graeca*† has been used throughout, and the action of these substances upon the coronary vessels determined by the direct and also by the perfusion methods already described.

Pituitary extracts.

The reaction of the blood vessels in the mammal to extracts of the pituitary body, or to the commercial preparations of this gland, have been extensively studied by other workers. The early observations of Oliver and Schäfer²³, in which they showed that an injection of pituitary extract causes an increased blood pressure and decreased cardiac rate, has been fully borne out and amplified by later observers^{2, 4, 15, 16}, especially by Dale⁵, using both the fresh extract of the gland and commercial preparations. All are in agreement that the peripheral blood vessels are constricted. Using the frog (*R. temporaria*), Krogh and his co-workers²¹, have shown that pituitrin‡

* Observations undertaken on behalf of the Medical Research Council.

† The experiments were performed during the months of December, January and February.

‡ The term pituitrin is used here and subsequently to indicate Parke Davis's preparation.

constricts the arteries of the web and foot, whether it be applied locally or perfused in very dilute concentration through the limb. Moreover, extirpation of the hypophysis in this animal, as Rehberg has shown²¹, gives rise within a few hours to a dilatation of the capillaries of the skin and web, which within twenty-four hours is very considerable. Krogh²¹, in fact, suggests as a result of further experiment that a pituitary hormone is normally present both in the amphibian and mammalian blood which is responsible for the tone of the capillaries.

With regard to the coronary arteries the observations have been confined to the mammalian heart. Pal²⁴, using an isolated strip of coronary artery, found that pituitrin brought about a definite constriction, a similar result being obtained by De Bonis and Suzanna⁹ using a fresh extract of the whole hypophysis. Cow³, also using the isolated artery, was unable to note any definite reaction to hypophysis extract; sometimes dilatation, at other time constriction being seen. Dale⁵, however, using an extract of the hypophysis, not only observed definite constriction in an isolated coronary strip, but also showed a diminished coronary outflow in the perfused rabbit's heart after adding the extract to the perfusion fluid. Rabe²⁵ using the hearts of rabbits, cats and dogs, could find no constant change in the coronary outflow upon introducing pituitary extract, sometimes dilatation, at others constriction, being produced.

Direct observation of the artery. The reaction to infundin* of the small arteries coursing upon the pulmonary artery in the intact heart, responding to regular induction shocks, has been observed directly in seven tortoises by the method described in a previous paper¹¹. Upon applying a drop of this substance to a small artery, this vessel quickly becomes much more distinct, and small adjacent arterioles and capillaries which were very indistinct before are now easily visible; the blood flow is greatly increased in all vessels covered by the drop. The reaction persists for fully thirty minutes and is limited to the area of application. If an artery is previously constricted to the point of disappearance by applying adrenalin in a dilution of 1 in 10,000, a drop of infundin subsequently placed upon the constricted vessel opens it up completely in a minute or two, and the blood flow is again seen. On one occasion several small superficial arteries were constricted by applying adrenalin to them, and these were quickly dilated when 0.1 cc. of infundin was injected into the aorta. In two tortoises a fresh extract of the pituitary body of the tortoise was used, the dissected gland being extracted with 3 drops of Ringer's solution. Local applications of a drop of such an extract gave similar results to those observed with infundin. The arteries coursing on the ventricle also reacted in a similar manner both to infundin and to freshly prepared extract of the tortoise pituitary body.

* Here and subsequently the term infundin applies to Burroughs, Wellcome and Co.'s preparation (17th, original extract).

The reaction does not appear to be limited to arteries of any special size, both the larger and smaller vessels dilating conspicuously. With regard to the capillaries, no final judgment could be passed, though on one occasion, when the flow in the coronary artery had been completely stopped by prolonged arrest of the heart, consequent upon vagal stimulation, the capillaries were seen definitely to dilate upon applying infundin locally to them, suggesting a specific action upon the capillary wall.

The general blood pressure was measured in two tortoises by inserting a cannula into the carotid artery and connecting it with citrated Ringer's solution to a mercury manometer. The injection of 0.1 cc. of infundin into the general circulation quickly reduced the blood pressure, in one case from 10 mm. Hg. to 0 mm. Hg., in the other from 30 mm. Hg. to 6 mm. Hg., the original pressures being later restored in each instance. The heart was driven throughout the observation by rhythmic shocks, at a rate slightly above the heart rate, and the ventricular systoles recorded. Slight decrease in the amplitude of the ventricular systole was seen during the observation. The coronary arteries in these two tortoises reacted in the usual manner to infundin.

Perfusion. The coronary artery was perfused in the manner detailed in the previous paper and the inflow measured before and after introducing infundin. The substance was injected into the tubing carrying the perfusion fluid to the heart in doses of 0.1 to 0.2 cc. of the full strength solution, or of 0.2 cc. of this solution diluted 100 or 1,000 times. The inflow into the coronary system was constantly increased whether the original strength or the dilution of 1 in 1,000 was employed, difference in degree with the different dilutions used alone being noted. The original rate of inflow was usually restored in 5-10 minutes, but, on occasions, a slightly increased rate persisted. The results of introducing infundin into the perfusion fluid are given in Table I. The ventricular and auricular systoles were always diminished during the height of the reaction, and occasionally the rhythmic stimuli became ineffective so that the heart beat with a very slow natural rhythm. As the reaction passed off, the systoles of both auricle and ventricle were, on occasions, greater than before the pituitary extract was introduced. In Fig. 1 a record resulting from an injection of 0.1 cc. of infundin is shown, the heart being driven rhythmically throughout at a rate of 18 per minute. At the beginning of the record the inflow amounts to 0.30 cc. per minute; immediately after the injection the inflow is increased and in the third minute amounts to 1.86 cc.; 21 minutes later it has fallen to 0.52 cc. per minute. The initial weakening and subsequent augmentation of both the auricular and ventricular systoles are clearly seen. On one occasion, 0.05 cc. of the extract of tortoise pituitary, prepared in the manner already described, was injected (see Table I, last column). The reaction was similar to that seen with infundin, the inflow being increased immediately after the injection and the original rate being restored in about 8 minutes. The systoles of the

Tortoise	J.	L.	S.	T.	M.	M.
Perfusion pressure in ems. H ₂ O	40	40	40	40	40	40
Rhythmic stim. per minute	37	27	18	22	27	27
	1.02	0.54	0.20	1.52	0.26	0.76
	1.09	0.56	0.28	1.40	0.28	0.78
	1.01	0.60	0.30	1.40	0.26	0.76
	0.98	0.62	Infundin	1.40	0.26	0.68
Infundin	0.1 cc.	0.15 cc.	0.1 cc.	1.36	Infundin	0.68
	1.44	0.98	1.56	0.2 cc.	0.2 cc.	Extract of tortoise
	1.27	1.70	1.86	1 in 100	0.48	hypophysis
	1.06	1.98	1.64	1.66	0.44	0.05 cc.
	1.05	1.80	1.36	2.30	0.42	0.88
	0.98	1.80	1.26	2.02	0.38	0.96
	1.02	1.76	1.16	1.54	0.36	0.80
		1.72	1.14	1.30	0.36	0.86
		1.76	1.00	1.20		0.82
		1.74	0.86	1.16		0.84
		1.70	0.76	1.16		0.80
			0.60	1.14		0.84
			0.52	1.14		0.76
			0.44	1.08		0.78
			0.52	1.04		0.80
			0.54	1.12		0.82
			0.52	1.12		
				1.02		
				0.96		

TABLE II.

*The influence of infundin upon coronary inflow (after atropinisation)***Inflow in ccs. per minute for successive minutes.*

Tortoise	P.	P. contd.	R.	R. contd.
Perfusion pressure in cms. H ₂ O	40		40	
Rhythmic stim. per min.	28		18	
	0.96	1.12	1.76	1.08
	0.96	1.16	1.66	1.20
	0.96	1.04	1.50	1.16
Atropine	Infundin	Atropine	Pressure raised	
0.15 mg.	0.2 cc.	0.1 mg.	to 45 cms. H ₂ O	
0.86	0.98	1.40	$\frac{1}{2}$ hour elapses	
0.76	0.80	1.56	1.60	
0.76	0.86	1.56	1.60	
0.74	1.02	1.46	Infundin	
0.66	1.14	1.32	0.1 cc.	
Infundin	1.26	Infundin	1.70	
0.2 cc.	1.28	0.1 cc.	1.70	
0.74	1.32	1.58	1.46	
0.60	1.36	1.76	1.34	
0.44	1.32	1.76	1.16	
0.60	1.34	Infundin	1.04	
0.64	1.32	0.1 cc.	1.10	
0.68	1.30	1.64	1.10	
0.78	1.32	1.96	1.00	
0.82	1.34	1.86	0.88	
0.96	1.26	1.68	0.98	
1.04		1.46	0.98	
1.08		1.32	1.00	
		1.32		
		1.26		
		1.20		

* Vagal stimulation was without effect upon the heart during these observations.

TABLE III.

*The influence of pituitary extracts upon coronary inflow (adrenalised vessels).**Inflow in ccs. per minute for successive minutes.*

Tortoise	E.	F.	H.	I.	X.
Perfusion pressure in cms. H ₂ O	45	45	45	30	45
Rhythmic stim. per min.	18	27	27	26	25
	0.66	0.76	0.26	0.46	0.32
	0.66	0.64	0.26	0.44	0.26
Pituitrin	0.68	0.26	0.26	0.44	0.26
0.3 cc.	Infundin	Infundin	Infundin	Infundin	Infundin
0.81	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.	0.1 cc.
0.97	0.88	0.28	1.60	0.60	
1.03	0.62	0.46	1.46	0.88	
1.09	1.60	0.84	1.36	1.18	
1.06	1.46	0.88	1.34	1.38	
1.01	1.46		1.28	1.36	
1.11	1.52		1.26	1.38	
1.16	1.52				
1.12	1.50				
1.15	1.04				
1.06	1.36				
	1.38				
	1.38				
	1.38				

Verschinin²⁶ has brought forward evidence, based upon the change in rhythm of the frog's heart, that atropine and pituitary extract act antagonistically, the extract directly stimulating vagal nerve endings. In the tortoise this would increase the flow by dilating the vessels, and the smaller increase in flow after atropine may be due to the loss of this effect. The fall in general blood pressure which occurs after injecting pituitary extract, accompanied as it is by little or no change in the force and by none in the rate of the rhythmically driven ventricle, indicates that the blood vessels generally are dilated.

Acetyl-choline.

The effect of introducing acetyl choline into the mammalian circulation has been extensively studied^{1, 6, 11, 17, 22}. Past observers find in general that apart from its action upon the heart, upon which organ it acts as a vagal stimulant, it definitely dilates the peripheral vessels: it lowers blood pressure when the cardiac action is so slightly weakened as to have a negligible effect. In the frog (*R. esculenta*) Koln and Pick¹⁹ noted a constriction of the leg vessels when these were perfused with Ringer solution to which acetyl-choline had been added. Krogh²⁰, on the other hand, was able to show a powerful dilator effect upon arteries of all sizes when acetyl-choline was applied in drops on the skin of *R. temporaria*, an observation also reported by Doi¹⁰ for the same animal. Very few observations appear to have been made upon the coronary artery. Eppinger and Hess¹³, using isolated strips of the mammalian coronary artery, found that acetyl-choline produced constriction.

Direct observation of the artery. Arteries directly observed under the microscope in the intact and rhythmically beating heart were seen definitely to dilate and the blood flow to increase within a minute or two after a drop of acetyl-choline, of a strength of 1 in 10,000 or 20,000, was placed upon them. The action persisted for 30 minutes or longer, and was very similar in degree to that seen after applying pituitary extracts locally. If the vessels were previously constricted by adrenalin, acetyl-choline locally applied to the constricted vessels opens them up within a minute or two. Arteries of all sizes reacted equally well.

The general blood pressure was measured in one tortoise. The injection of 0.2 cc. of 1 in 2,000 solution acetyl-choline lowered the blood pressure quickly from 20 mm. Hg. to 8 mm. Hg.. Within 15 minutes the blood pressure was again 20 mm. Hg.. The heart was driven throughout by rhythmic break shocks and the ventricular systoles recorded; no change was seen in the ventricular systoles during this observation.

Perfusion. Small amounts of acetyl-choline in a strength of 1 in 20,000* were introduced into the tubing carrying the perfusion fluid to the coronary

* A solution of 5.0 mgms. of acetylcholine chloride in 1 cc. of absolute alcohol was diluted as desired with Ringer's solution and used fresh at each injection.

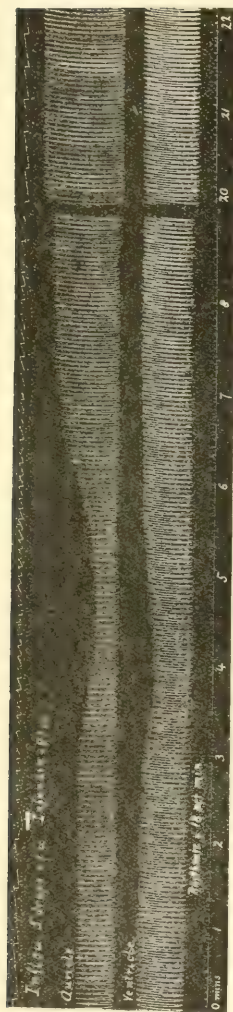


Fig. 1 (7.18). Tortoise S. Effect upon coronary inflow of introducing 0.1 cc. infundin into perfusion fluid.
Perfusion pressure = 40 cms. H_2O . Time marker = 5 sec.



Fig. 2 (7.18). Tortoise Y. Effect upon coronary inflow of introducing normal m/z. acetylcholine into perfusion fluid.
Perfusion pressure = 45 cms. H_2O . Time marker = 5 sec.

artery in three tortoises. The constant reaction is an immediate and slight increase in coronary inflow; the reaction lasts about 5-6 minutes, after which the original inflow is again restored (Table IV).

The auricular systoles were diminished by the injection, the systoles of the ventricle, responding to rhythmic break shocks, remaining unchanged. In Fig. 2 is shown a record of an injection of 0.00001 mgm. of acetyl choline into the perfusion fluid. The coronary inflow at the beginning is 0.74 cc. per minute, immediately after the injection it rises to 1.0 cc. per minute, and within 7 minutes the original rate of inflow is again restored. The ventricle, driven by rhythmic shocks at 23 per minute, remains unchanged throughout, while the auricular systoles are diminished coincident with the

TABLE IV.

The influence of acetylcholine upon coronary inflow.
Inflow in cc. per minute at successive minutes.

Tortoise	X.	Y.	Z.	W.
Perfusion pressure in cms. H ₂ O	45	45	40	45
Rhythmic stim. per minute	22	23	23	25
			1.08	0.72	1.00	Atropine
			1.02	0.78	0.94	0.1 mg.
			0.90	0.74	0.94	0.96
			Ac. Ch. 0.2 cc.	Ac. Ch. 0.2 cc.	Ac. Ch. 0.1 cc.	0.94
			1 in 20,000	1 in 20,000	1 in 20,000	0.94*
			1.02	0.86	0.98	Ac. Ch. 0.1 cc.
			1.26	0.96	1.72	1 in 20,000
			1.26	1.00	1.84	0.96
			1.08	0.98	1.58	0.94
			0.96	0.88	1.28	0.96
			0.84	0.82	1.16	0.94
			0.80	0.80	1.04	0.88
			Ac. Ch. 0.1 cc.	0.72	0.96	0.88
			1 in 20,000	0.78	0.96	0.88
			0.82	0.76	0.92	0.88
			1.02	0.76	0.82	0.92
			1.14	0.76	0.90	0.88
			1.06	0.76	0.86	0.94*
			0.94	0.76	0.96	0.96
			0.90	Ac. Ch. 0.02 cc.	Atropine	Ac. Ch. 0.1 cc.
			0.80	1 in 20,000	0.1 mg.	1 in 20,000
			0.86	0.88	0.96	0.88
			0.82	0.94	1.06	0.90
			Ac. Ch. 0.2 cc.	0.90	1.20	0.86
			1 in 20,000	0.82	1.16	0.92
			0.82	0.80	1.12*	0.90
			1.32	0.82	1.20	
			1.36		Ac. Ch. 0.1 cc.	
			1.16		1 in 20,000	
			1.00		1.24	
			0.96		1.22	
			1.04		1.22	
			1.00		1.26	
					1.22	

* Vagal stimulation without effect upon the heart.

acceleration of the coronary inflow. In three tortoises, an increased inflow having been obtained after an injection of acetyl-choline, atropine sufficient to paralyse completely the vagal nerve endings was given. Subsequent injections of acetyl-choline had, under these circumstances, no effect either on the inflow or on the auricular systole. The results of acetyl-choline injections are given in Table IV.

Acetyl-choline constantly dilates the coronary vessels, the degree being similar to that seen in the best examples of vagal stimulation. As its action is completely abolished by atropine it may be said to exert its effect entirely upon the vagal nerve endings. The lowering of blood pressure, which is produced by an injection, though the ventricular rate and systole be maintained unchanged would indicate that in the tortoise, as in the mammal and frog, acetyl-choline is a general vasodilator.

Histamine.

The influence of histamine upon the arterial system in mammals has been carefully investigated by Dale and his co-workers^{6, 7, 8}. They find that the reaction varies in different species. In the cat, dog, fowl and monkey, the blood pressure is lowered, the cardiac rate and ventricular systole being slightly augmented at the same time. This fall of blood pressure in the cat is brought about by dilatation of the capillaries, the arterioles being slightly constricted at the same time. In the rabbit and guinea pig, however, a rise of blood pressure is generally seen, consequent, so it is believed, upon the arteriolar constriction not being associated with a dilatation of the capillaries. Doi¹⁰, using the frog, found the web vessels to dilate after an intravenous injection, but Krogh²¹ has been unable to obtain any certain evidence of dilator activity either when injecting the drug into the web or when applying it to the surface; while Dale⁶ reports a small rise of blood pressure after an injection into the general circulation. With regard to the coronary system, Dale⁶ has shown in a perfused rabbit's heart that the coronary outflow is lessened after the introduction of histamine, the cardiac rate and systole being increased at the same time. Rabe²⁵ has been unable to determine any constant change to histamine in the coronary outflow in the cat, both increase and decrease being recorded. Dale's observation, however, has been confirmed by Krawkow¹⁸.

Direct observation of the artery. When a small artery, either on the pulmonary artery or coursing in the ventricle, was observed in the intact heart responding to rhythmic stimulation, and a drop of 1 in 30,000 solution of histamine* was placed upon it, the vessel quickly dilated and the blood flow increased. The reaction occurred within two minutes and passed off in about half-an-hour. Vessels previously constricted by adrenalin were

* Dilution of histamine base; Burroughs, Wellcome and Co's. Ergamine acid phosphate being used.

quickly dilated by a local application of histamine. Arteries of all sizes were equally affected but no definite opinion could be formed as to the action upon the capillaries. In one experiment the injection of 0.4 cc. of 1 in 30,000 histamine into the blood stream, lowered the general blood pressure from 34 mm. Hg. to 16 mm. Hg.; while in a second experiment the same dose lowered it from 20 mm. Hg. to 6 mm. Hg., the original blood pressures being restored later. In both experiments, the heart was driven rhythmically by means of break shocks, and the ventricular systoles recorded; no change in ventricular systole was seen after the injection.

Perfusion. In two tortoises, injections of histamine were made into the perfusion fluid. In both cases, either with a strong dose (1 cc. of a 1 in 3,000 solution) or with a weaker dose (0.2 cc. of a 1 in 30,000), the coronary inflow was immediately increased, difference in degree being alone noted.

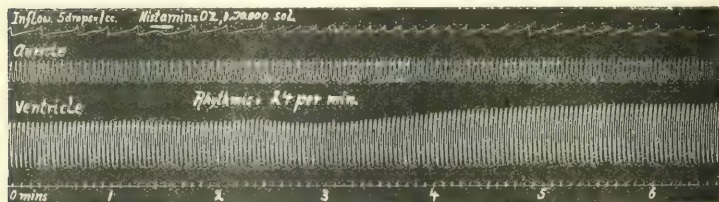


FIG. 3 (511). Tortoise X. Effect upon coronary inflow of introducing 0.2 cc. of a 1 in 30,000 solution of histamine into perfusion fluid. Perfusion pressure = 45 cms. H_2O . Time marker 5 secs.

The reaction was usually slightly delayed, lasted about five minutes, after which the original rate of inflow became restored (Table V). In Fig. 3 is a record of an injection of 0.2 cc. of histamine of 1 in 30,000 dilution; at the beginning of the record the inflow amounts to 0.68 cc. per minute; about 1 minute after the injection the inflow is increased to 1.5 cc. per minute, the original rate of flow being restored in about 4 minutes. The ventricle was driven rhythmically throughout at a rate of 24 per minute, and the ventricular systoles show a slight augmentation at the end of the record; this effect is inconstant, however. The auricular beats remain unchanged throughout. In two tortoises sufficient atropine was injected to paralyse completely the vagal nerve endings; the reaction to histamine remained unchanged.

Histamine is found constantly to dilate the coronary vessels and acts equally well upon the larger or smaller vessels. Its dilator action is unaffected by previous atropinisation, and is consequently not due to vagal stimulation. The fall of blood pressure consequent upon an injection into the general circulation indicates a general vasodilatation, the ventricular rate and systole being maintained unchanged.

TABLE V.

The influence of histamine upon coronary inflow. Inflow in ccs. per minute for successive minutes.

Tortoise...	...	W.	X.	X contd.	Z.	W.
Perfusion pressure in cms. H ₂ O		45	45		45	45
Rhythmic minute	stim. per	25	24		24	25
		0.56	0.66	Histamine	Atropine	1.00
		0.56	0.76	0.1 cc. 1 in	0.1 mg.	1.00
		0.56	0.68	30,000	1.66	Atropine
	Histamine	Histamine	0.98	1.76	0.1 mg.	1.00
	1 cc. 1 in	0.2 cc. 1 in	1.22	1.68*	1.00	1.00
	30,000	30,000	1.06	1.66	0.96	0.98*
	0.56	0.84	0.78	Histamine		
	1.12	1.50	0.76	1 cc. 1 in	Histamine	
	1.82	1.24	0.76	30,000	1 cc. 1 in	3,000
	1.80	0.86	0.78	1.14	1.00	
	1.52	0.86	0.78	1.38	0.86	
	1.38	0.96	0.76	2.00	1.10	
	1.26	0.94	0.76	2.16	1.54	
	1.22	0.90	0.72	2.20	1.56	
	1.12	0.88		2.16	1.56	
	1.14	0.86		2.12	1.46	
	1.06	Histamine		2.00	1.24	
	1.06	0.2 cc. 1 in		2.00	1.10	
	1.04	30,000		2.02	1.10	
	1.04	1.18		2.04		
	1.04	1.42				
	1.04	1.16		5 minutes		
	5 minutes	0.92		elapse		
	1.16	0.86		1.88		
	1.16	0.88		1.84		
	Histamine	0.88				
	1 cc. 1 in	0.88				
	30,000	0.86				
	1.38	0.84				
	1.84	0.90				
	1.98	0.84				
	1.74	0.84				
	1.38	0.88				
	1.44					
	1.04					
	1.00					

* Vagal stimulation without effect upon the heart.

CONCLUSIONS.

The coronary arteries of the tortoise are constantly dilated by pituitary extracts, acetyl-choline, and histamine. This reaction occurs whether the substance is applied locally to the superficial coronary arteries in an intact heart beating at constant rate, or is added to Ringer's solution used to perfuse the coronary vessels.

Full atropinisation of the tortoise abolishes the vasodilator action of acetyl-choline, decreases in slight degree the dilatation produced by pituitary extracts, but has no effect upon the histamine dilatation.

The general blood pressure is lowered by each of the substances when these are introduced into the general circulation: this happens even if the ventricular rate is maintained constant. The ventricular systole is slightly weakened by pituitary extracts, occasionally augmented by histamine, and unaffected by acetyl-choline.

My grateful acknowledgments are due to Dr. A. N. Drury, who has given me material assistance in these observations.

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THE INFLUENCE OF CIRCULATORY DISTURBANCES ON THE GASEOUS EXCHANGE OF THE BLOOD.

V.—THE BLOOD GASES AND CIRCULATION RATE IN HYPERTHYROIDISM.

By H. WHITRIDGE DAVIES, JONATHAN MEAKINS and
JANE SANDS.

(From the Department of Therapeutics, University of Edinburgh.)

IN hyperthyroidism there are signs which indicate a disturbed cardio-vascular system. The most obvious of these are tachycardia under resting conditions and pronounced increase of heart rate with dyspnoea on exertion. These responses also occur in normal people on physical exertion, although the amount of effort necessary to induce them in hyperthyroidism is much less. In view of the well established fact that in hyperthyroidism there is a conspicuous increase in the basal metabolic rate, it seemed of importance to determine what changes might occur in the gaseous exchange of the blood and the general circulation rate. Hyperthyroidism is peculiar in being the only condition, other than the physiological state of the body under exercise, in which there is an increased metabolism and, seemingly, an overacting circulatory system. For the purpose, thirteen cases of exophthalmic goitre and two cases of toxic adenoma of the thyroid have been investigated and in six of these cases a comparison has been instituted between the condition before and after partial thyroidectomy. The chief details of these cases are contained in the protocols at the end of this paper.

Gases of the arterial blood.

In cases of uncomplicated hyperthyroidism it was found that the hæmoglobin of the arterial blood was saturated to between 96-97 per cent. with oxygen. The values were obviously in the upper limits of normality, and rendered it expedient to investigate the oxy-hæmoglobin curves in these cases. These were found to be situated slightly more to the left than in the average normal curve, indicating a somewhat heightened capacity of the blood to combine with oxygen, but not greater than has been recorded of some normal bloods. The average curve lay slightly to the left of that

reported by Barcroft¹, both curves corresponding to 40 mm. carbon dioxide pressure. It might suggest the presence in the arterial blood of a slight degree of relative alkalosis.

TABLE I.
*Carbon dioxide pressure in the alveolar air in case of
hyperthyroidism.*

Case.	Alveolar CO ₂ in mm. Hg.	Remarks.
1	18.0 20.0	Before operation. After ..
2	18.0 14.8	Before .. After ..
3	35.7 32.8	Before .. After ..
4	41.7 39.2	Before .. After ..
5	37.6	Before ..
6	36.4 32.0	Before .. After ..
7	41.4	Before ..
8	36.4	Before ..
9	28.5	Before ..
10	31.4	Mitral stenosis.
11	32.0	Before operation.
12	32.0	Before ..
13	40.0 39.2	Before .. After ..
14	35.8	Before ..
15	32.0	Before ..
16	40.0	Max. dose of thyroid extract.

The carbon dioxide content of the arterial blood was found to be equal to the average normal, namely, 50 to 51 volumes per cent.. In four cases it was found to be within these limits and in two it was 51.8 and 52.3 volumes per cent. respectively. The carbon dioxide dissociation curves were determined to ascertain whether any obvious change in the carbon dioxide combining power or "alkali reserve" of the blood exists. The blood so examined was obtained from the median basilic or cephalic veins without inducing stasis, or otherwise changing the local circulation. The blood

was immediately examined and every care taken to avoid glycolysis. It is evident from Fig. 1 that the carbon dioxide dissociation curves of the six cases examined fall very close to the curve published by Douglas and Haldane. Their dissociation curve represents in our experience also that of the average normal individual.* Curves published by other investigators would indicate, however, that their curve is somewhat to the left of the average normal. One of a number of factors might depress a normal curve, and unless these are scrupulously avoided curves obtained by different workers may not be comparable. It may be taken, therefore, that the "alkali reserve" of the cases examined falls well within the normal limits.

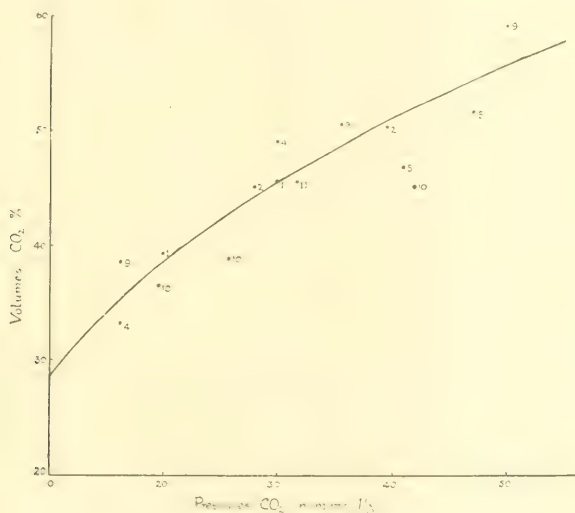


Fig. 1. Carbon dioxide-containing power increases of deranged thyroid function. (Figures refer to number of case in protocol.)

The partial pressure of the gases in the alveolar air was determined by the Haldane-Priestley method. The oxygen partial pressure ranged from 103 to 110 mm. Hg. In view of the obvious hyperpnea that was present even at rest, these findings were considered quite in accord with the increased saturation of the oxy-haemoglobin of the arterial blood and the slight elevation of the oxy-haemoglobin dissociation curve.

* This is corroborated by the curves obtained by Peters, Barr and Rule in three normal people. (4.)

The carbon dioxide partial pressure in the alveolar air is shown in Table I. It was found that the partial pressure closely approximated to or was above the average normal, which is 37-40 mm. Hg. before operation, while after operation it was uniformly decreased by comparison.

Blood flow per minute. The minute volume output of the heart was determined by the method described by Meakins and Davies³. It was generally found in these hyperthyroidism cases to be increased. After the symptoms had subsided, either as a result of medical or surgical treatment, it was found that the minute volume had decreased to an approximately normal level.

The subjects at the time of the determinations of the minute volume* were not under basal conditions, all estimations being made a few hours after the mid-day meal and under approximately the same conditions of rest throughout. It was impossible to carry out the numerous and consecutive observations necessary and at the same time to maintain the patients under basal conditions. The minute volumes and estimates of metabolism are set forth in Table II.

In general the decrease of metabolism coincided with the reduction in the minute volume. In some cases the variations were not pronounced while in others they were conspicuous. This is particularly obvious in Cases 11 and 14 in Table II. A complete parallelism between the two in different cases could not be traced. On the whole, however, the changes in minute volume and metabolism appeared to be in the same direction and more or less proportional.

In order to substantiate this conclusion a statistical study has been made of the data of Table II. The average minute volume is calculated at 7.21 litres per hour, and the average calories per square metre per hour is 58.31. The standard deviation of the minute volume is 1.84, and the coefficient of variability 25.5, while the standard deviation for calories per square metre per hour is 13.29, and the co-efficient of variability is 22.8. The correlation of minute volumes and calories per square metre per hour is 0.726, the probable error being 0.044. The co-efficients of variation are not unduly large, especially if one considers that the data include pre-operative and post-operative cases with conspicuous changes in both minute volume and metabolism. Thus, these values substantiate the conclusion that the general blood flow varies directly with metabolism.

The correlation is shown graphically in Fig. 2. This figure is a scatter diagram of the mean deviation divided by the standard deviation of the blood flow per minute and the calories per square metre per hour. The results are plotted in relation to each other. It will be seen that eighty-four per cent. of the observations fall in a comparatively narrow zone enclosed by the diagonal lines.

The increase of blood flow (through the arms at least) was confirmed by the high oxygen saturation of the venous blood as obtained from the median basilic vein. This was found to be between 75 and 80 per cent. saturated, and in several cases was as much as 85 per cent. saturated.

* The minute volume in this paper refers to the volume of blood passing through the heart per minute.

The method of estimating the minute volume of the arterial blood by multiplying the pulse rate by the pulse pressure (as determined by auscultation) was correlated with the blood flow as estimated by the respiratory method. The correlation was found to be 0.29, while the probable error was 0.11. It is, therefore, evident that there is no correlation between these series of data.

TABLE II.

Blood flow per minute, pulse rate, blood pressure and metabolism in cases of thyroid disease.

Case.	Age.	Blood flow in litres per min.	Pulse rate per min.	Systolic output in cc. per beat.	Calories per sq. mm. per hr.	Blood pressure in mm. Hg.			Remarks.	Date.
						S.	D.	P.P.		
1	25	8.70	108	84	54.4	--	--	--	Before operation	10/5/23
		8.94	104	86	—	—	—	—	" "	17/5/23
		4.94	100	49	45.0	125	85	40	After "	19/6/23
		4.00	90	44	42.0	120	85	35	" "	24/6/23
2	26	8.08	113	72	60.9	135	75	60	Before operation	16/4/23
		6.87	106	65	63.0	—	—	—	" "	23/4/23
		4.13	83	51	40.67	—	—	—	After "	23/6/23
3	20	4.67	100	47	48.26	120	85	35	Before operation	4/10/23
		6.30	106	60	53.87	120	78	42	" "	19/10/23
		5.90	104	48	55.50	—	—	—	" "	22/10/23
		3.50	94	37	39.69	90	45	45	After "	10/4/24
4	35	9.26	106	87	55.40	—	—	—	Before operation	4/7/23
		7.63	90	85	55.34	—	—	—	" "	5/7/23
		7.17	90	80	54.75	—	—	—	" "	10/7/23
		8.69	102	85	53.22	140	60	80	" "	16/7/23
		5.84	74	79	33.77	—	—	—	After "	8/8/23
		5.27	78	68	40.20	135	90	45	" "	21/9/23
		5.15	68	76	38.13	—	—	—	" "	22/9/23
5	18	5.40	108	50	—	—	—	—	Before operation	29/9/23
		5.58	120	47	52.26	132	80	52	" "	25/10/23
6	37	7.45	118	63	72.57	140	84	56	Before operation	29/9/23
		6.65	112	59	51.54	142	95	47	" "	17/1/24
		6.60	112	59	68.74	135	85	50	After "	7/4/24
7	25	9.2	132	70	71.73	—	—	—	Before operation	21/9/23
		8.87	118	75	61.60	—	—	—	" "	27/9/23
		9.17	112	82	61.75	145	55	90	" "	5/10/23
		8.05	104	79	69.98	145	75	70	" "	10/10/23
		7.70	100	77	69.02	—	—	—	" "	17/10/23
8	22	7.74	110	72	52.76	—	—	—	Before operation	20/9/23
		8.40	120	70	50.36	132	80	52	" "	1/10/23
		7.30	104	70	43.02	—	—	—	" "	11/10/23
		8.58	122	70	65.36	148	90	58	" "	25/10/23
		6.93	102	68	57.40	140	80	60	" "	14/11/23
9	19	8.87	93	95	—	—	—	—	No operation	31/5/22
		8.50	96	86	—	—	—	—	" "	1/6/22
		8.18	95	86	61.37	—	—	—	" "	20/6/22
10	46	9.15	83?	110?	59.71	—	—	—	Auricular	8/10/23
		8.68	92?	94?	63.68	—	—	—	fibrillation	9/10/23
		7.30	92	80	57.20	—	—	—	Normal rhythm	17/11/23
		7.90	92	87	63.28	140	90	50	" "	19/11/23
11	18	10.35	160	65	80.32	100	55	45	Before operation	25/3/24
		8.47	134	63	68.34	130	85	45	" "	28/3/24
12	30	11.54	120	96	100.60	145	67	78	Before operation	24/3/24
		10.8	108	100	80.78	140	64	76	" "	27/3/24
13	31	7.60	116	66	56.62	137	98	39	Before operation	17/12/23
		7.26	120	60	57.54	140	88	52	" "	18/12/23
		5.46	96	57	50.10	145	100	45	After "	9/4/24
14	35	10.00	119	84	87.94	122	58	64	Before operation	20/12/23
		7.94	100	79	74.27	127	50	77	" "	21/12/23
		7.70	102	75	73.94	124	50	74	" "	28/12/23
		7.66	98	78	65.91	129	65	64	" "	31/12/23
15	45	6.33	90	70	53.67	185	120	65	Before operation	17/3/24
		7.75	100	77	52.32	190	135	55	" "	20/3/24
16	18	4.10	84	49	43.24	—	—	—	Post operative	12/6/22
		4.12	86	48	—	—	—	—	myxoedema	13/6/22
	19	5.04	104	48	40.61	—	—	—	On thyroid extract	14/7/22
		4.48	96	47	—	—	—	—	" "	17/9/23
		4.55	97	46	—	—	—	—	" "	18/9/23

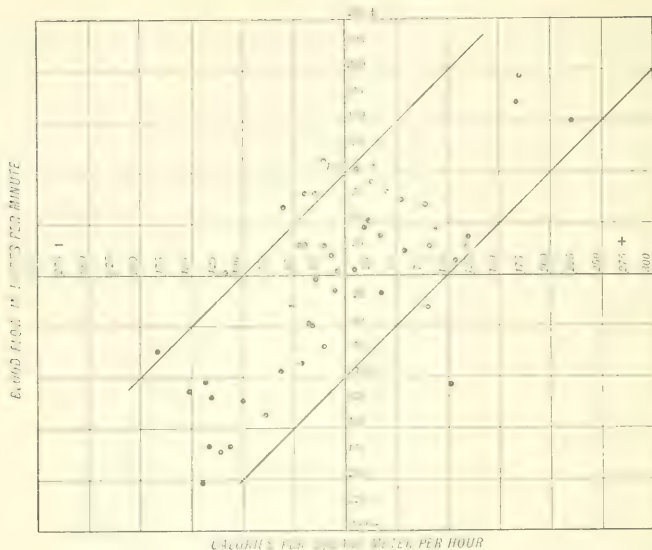


Fig. 2. Scatter diagram from a comparison of the mean deviations divided by the standard deviations of blood flow in litres per minute, and calories per square metre per hour taken from Table II.

It will be noted in regard to the output per heart beat that there is some variation from case to case: the variation is greatest in the estimates of the pre-operative stage, the output per beat always declining after operation. The decline is attributed to the diminished requirements of the circulation resulting from lower metabolic rate. A somewhat similar condition has been described by Barcroft and Marshall: they found that the cardiac rate and output per beat both decreased after prolonged rest.

The changes in output per heart beat on June 10 are doubtful. It was difficult to be certain of the average cardiac rate during the period of auricular fibrillation. Although frequent pulse records were taken during the periods occupied by the tests, the average rates obtained were only approximate. Case 16 was one of post-operative hypotension. It has been included in the present series as it was found possible to vary the basal metabolic rate from minus 40 per cent. to plus 20 per cent. During the period when her circulation rates were estimated her metabolism was always above the normal for her size and age.

Protocols of Cases.

Case 1. Female, aged 25, admitted April the 18th, 1923, complaining of weakness, breathlessness and swelling of the throat of nine months' duration. She had periodic flushings of the face, tachycardia and uniform enlargement of the thyroid; a pulse rate of 106, thyroid thrill, vigorous pulsation in the arteries. The heart not enlarged; the blood pressures were 124 (systolic), 70 (diastolic). Body surface was calculated at 1.49 square metres. Basal metabolic rate was plus 45 per cent.. Partial thyroidectomy was successfully undertaken on June the 7th, 1923. Organ found hyperplastic and not adenomatous. Within a few weeks the basal metabolic rate was reduced to plus 3 per cent. and the patient has remained in good health since.*

Case 2. Female, aged 26, admitted July the 22nd, 1922, complaining of swelling of the neck and nervousness. She had evidently lost considerable weight. Periodic flushing, dyspnoea, enlargement of the thyroid, particularly of the right lobe and isthmus over which was a thyroid thrill and diffuse precordial pulsation were present. Heart not enlarged. There was exophthalmos and fine tremor of the hands. Blood pressures were 124 (systolic), 66 (diastolic); heart rate 124. Body surface was calculated at 1.41 square metres. Basal metabolic rate varied from plus 40 per cent. to plus 90 per cent.. On May the 30th, 1923, the right lobe and isthmus of the thyroid were removed. The organ showed diffuse hyperplasia but no adenomatosis. Within a few weeks the basal metabolic rate had returned to normal and the patient has remained in good health.

Case 3. Female, aged 20, admitted September the 21st, 1923, complaining of swelling of the neck, palpitation and breathlessness on exertion, and swelling of the ankles at night, of three or four years' duration. She showed pronounced general flushing and perspired freely. There was moderate exophthalmos, very fine tremor, and the heart was slightly enlarged. Heart rate was 100 per minute. Blood pressures were 110 (systolic), 55 (diastolic). Body surface was calculated at 1.60 square metres. Basal metabolic rate varied from plus 8 per cent. to plus 70 per cent.. On March the 4th, 1924, thyroidectomy was successfully undertaken. The organ was hyperplastic but not adenomatous. A month after operation the basal metabolic rate had returned to normal and the patient has remained in good health since.

Case 4. Female, aged 35, admitted March the 27th, 1923, complaining of a strained feeling of the eyes and dragging of the lids, swelling in the neck, and nervousness, of about three months' duration. The thyroid was symmetrically enlarged and there was a faint thyroid thrill, with sweating and general flushing and little exophthalmos. Heart slightly enlarged; heart rate 130. Blood pressures were 130 (systolic), 55 (diastolic). Body surface calculated at 1.45 square metres. The basal metabolic rate varied from plus 27 per cent. to plus 70 per cent.. On July the 24th, 1923, thyroidectomy was successfully done. The organ showed a diffuse hyperplasia but no adenomata were found. At the end of a month the basal metabolic rate was minus 19 per cent., but since then has returned to normal and the patient has continued in good health.

Case 5. Female, aged 18, admitted September the 20th, 1923, complaining of swelling of the neck of four years' duration. There was exophthalmos, dyspnoea on exertion, tremor of the hands, enlarged thyroid, particularly the right lobe, and a thyroid thrill and systolic bruit. Heart was moderately enlarged; heart rate 110. Blood pressures were 120 (systolic), 58 (diastolic). Body surface calculated at 1.69 square metres. Basal metabolic rate varied from plus 12 per cent. to plus 46 per cent.. The patient developed acute encephalitis lethargica and died on November the 28th, 1923. No post-mortem examination.

Case 6. Female, aged 37, admitted September the 8th, 1923, complaining of goitre, nervousness and trembling, of three years' duration. There was slight exophthalmos, uniform enlargement of the thyroid with a thyroid thrill and bruit, and vigorous pulsation in the carotids. Heart was slightly enlarged; heart rate 114. Blood pressures were 116 (systolic), 65 (diastolic). Body surface calculated at 1.44 square metres. The basal metabolic rate varied from plus 25 per cent. to plus 45 per cent.. On March the 13th, 1924, partial thyroidectomy was done. The organ was hyperplastic but no adenomata were found. After six weeks the basal metabolic rate was still plus 21 per cent.. Since then there has been only a moderate decrease in the symptoms.

Case 7. Male, aged 25, admitted September the 13th, 1923, complaining of nervousness, sweating, and tachycardia on exertion, of three years' duration, dating from an attack of lobar pneumonia, during which exophthalmos appeared suddenly. He showed pronounced exophthalmos, fine temper of the hands, the thyroid was enlarged, particularly on the right side. There was a thyroid thrill and pulsation of the carotids. Heart was moderately enlarged; heart rate 90 per minute. Blood pressures were 120 (systolic), 65 (diastolic). Body surface calculated at

* Macroscopic and histological examination was done in each case in which thyroidectomy was performed.

1.80 square metres. Basal metabolic rate was plus 16 per cent.. On October the 23rd, 1923, thyroidectomy undertaken. October the 24th, 1923, patient died suddenly. The organ showed diffuse hyperplasia without evidence of adenomata.

Case 8. Female, aged 22, admitted July the 30th, 1923, complaining of swelling in the neck, leanness, palpitation, breathlessness and prominence of the eyes of seven months' duration, following an acute attack of follicular tonsillitis. There was moderate exophthalmos, slight tremor of the hands, uniform enlargement of the thyroid with a systolic thrill and bruit over both lobes. Heart was moderately enlarged and the heart rate was 110 per minute. Blood pressures were 140 (systolic), 70 (diastolic). Body surface calculated at 1.58 square metres and the basal metabolic rate varied from plus 8 per cent. to plus 52 per cent.. On November the 16th, 1923, thyroidectomy was done. Organ was found hyperplastic but not adenomatous. One month after operation the basal metabolic rate was minus 1 per cent. and since then the patient has remained in good health.

Case 9. Male, aged 19, admitted May the 8th, 1922, complaining of sweating, nervousness, prominence of the eyes and swelling of the neck, of one year's duration. Slight exophthalmos, no obvious thyroid enlargement. Heart was not enlarged; heart rate 90 per minute. Blood pressures were 115 (systolic), 50 (diastolic). Body surface calculated at 1.71 square metres. Basal metabolic rate varied from plus 15 per cent. to plus 57 per cent.. Patient was discharged from hospital without operation.

Case 10. Male, aged 46, admitted September the 28th, 1923, complaining of edema of the legs and swelling of the abdomen of two months' duration. Six years previously he had had swelling of the neck, protrusion of the eyes, nervousness, breathlessness and flushing. On rest he improved, but three or four months later an exacerbation occurred. He has had remissions and exacerbations during the past six years. On examination he showed orthopnea, cyanosis of face and hands, moderate exophthalmos, uniform enlargement of the thyroid. No thyroid thrill. Heart was moderately enlarged; pulse weak and irregular. There was mitral stenosis and auricular fibrillation. On treatment with digitalis and quinine the normal rhythm was established when the heart rate was 80 per minute. Blood pressures were 160 (systolic), 93 (diastolic). The body surface was calculated at 1.77 square metres. The basal metabolic rate varied from plus 23 per cent. to plus 77 per cent.. Patient refused operation although on February the 29th, 1924, the basal metabolic rate was plus 77 per cent.. The cardiac rhythm was normal, and patient stated he felt perfectly well and was working every day.

Case 11. Female, aged 18, admitted March the 19th, 1924, complaining of swelling of the neck and breathlessness on exertion of three months' duration. There was exophthalmos, uniform enlargement of the thyroid, slight tremor and flushing. The heart was slightly enlarged; heart rate 140 per minute. Blood pressures were 128 (systolic), 90 (diastolic). Body surface calculated at 1.46 square metres. The basal metabolic rate was plus 48 per cent.. Lugol's iodine, minims X three times a day, was given with pronounced temporary improvement. Patient refused operation.

Case 12. Male, aged 30, admitted January the 28th, 1924, complaining of swelling of the neck, nervousness, protrusion of the eyes, breathlessness and trembling, of seven months' duration. There was pronounced exophthalmos, fine tremor of the hands, the thyroid enlargement, particularly on the right side, and a pronounced thyroid thrill and bruit. The heart was slightly enlarged and there was a rough systolic murmur transmitted to the axilla. Heart rate 96 per minute. Blood pressures 140 (systolic), 50 (diastolic). Body surface calculated at 1.74 square metres. Basal metabolic rate was plus 54 per cent.. Patient was put on Lugol's iodine minims X three times a day, which produced pronounced but temporary improvement, the basal metabolic rate being reduced to plus 18 per cent.. Operation on June the 21st, 1924, when the greater part of the thyroid was removed. The organ was found to be hypoplastic but not adenomatous.

Case 13. Female, aged 31, admitted November the 7th, 1923, complaining of noises in the ears, prominence of the eyes, swelling of the neck, of eight months' duration. There was palpitation on exertion, moderate exophthalmos, skin flushed easily and there was pronounced tremor of the hands. Heart was moderately enlarged and there was a systolic murmur heard over a wide area at the apex. Blood pressures were 150 (systolic), 75 (diastolic). Moderate uniform enlargement of thyroid. Body surface calculated at 1.45 square metres. Basal metabolic rate varied from plus 17 per cent. to plus 39 per cent.. On December the 18th, 1923, thyroidectomy was successfully undertaken. The organ showed pronounced hyperplasia, but no adenomata. After operation the basal metabolism fell to minus five per cent., but after several months returned to plus 16 per cent.. Since then it has not gone above this point and patient is free of symptoms.

Case 14. Female, aged 35, admitted December the 17th, 1923, complaining of cough, swelling of the neck and protrusion of the eyes, of three months' duration. On closer questioning it was revealed that for twelve years she had been suffering from increasing nervousness with

palpitation and dyspnoea on exertion; also she was becoming progressively more emotional and there had been a steady loss of weight during this period. Heart was moderately enlarged; heart rate was 130 per minute. Blood pressures were 150 (systolic), 65 (diastolic). The body surface was calculated at 1.40 square metres. The basal metabolic rate was found to vary from plus 53 per cent. to plus 109 per cent.. There was irregular enlargement of both lobes of the thyroid. On February the 19th, 1924, partial thyroidectomy, right lobe, was undertaken. The patient did well until February the 21st, 1924, when auricular fibrillation developed, and she died suddenly on February the 22nd, 1924. Portion of the thyroid removed was very hyperplastic, and contained an encapsulated adenoma about 3.5 cm. in diameter.

Case 15. Female, aged 43, admitted March the 11th, 1924, complaining of tiredness, dizziness, palpitation, breathlessness and nervousness of 28 years' duration. 20 years before, partial thyroidectomy had been done and following this there was pronounced improvement until six years ago, when the symptoms began to get gradually worse. In the neck a freely movable round nodule 3 cm. in diameter was found. No exophthalmos and slight tremor. Heart was definitely enlarged; heart rate 95 per minute. Blood pressures were 175 (systolic), 110 (diastolic). The body surface was calculated at 1.66 square metres, and the basal metabolic rate was plus 54 per cent.. On April the 1st, 1924, thyroidectomy was successfully undertaken. The organ was found to contain numerous adenomata, but was not hyperplastic.

Case 16. Female, aged 17, admitted May the 20th, 1922, complaining of breathlessness and delayed onset of puberty. Right-sided thyroidectomy at seven years of age, and left-sided thyroidectomy at 15 years of age, had previously been done. Since the last operation patient had ceased to grow, and had become stouter and asthenic. Features were coarse, lips thick, skin dry, speech slow, intelligence deficient, hands thick, short and coarse. Heart was not enlarged; heart rate 60 per minute. Blood pressures were 90 (systolic), 60 (diastolic). Body surface calculated at 1.21 square metres. Basal metabolic rate was minus 40 per cent.. On thyroid extract the basal metabolism increased to plus 20 per cent., and during a period of a year-and-a-half, it could be varied from plus 20 per cent. to minus 16 per cent.. During this time she grew 2 inches, gained 12½ lbs. in weight, had no dyspnoea, and menstruation began after a few months and continued regularly. Diagnosed as post-operative myxedema.

CONCLUSIONS.

1. The oxy-hæmoglobin and the carbon dioxide dissociation curves in hyperthyroidism are approximately normal.
2. The partial pressure of carbon dioxide in the alveolar air is uniformly higher during periods of active hyperthyroidism than during periods when thyroid function is relatively normal.
3. The minute volume output of the heart is increased in proportion to the increase of metabolism, the two being closely correlated.
4. The systolic output per beat of the heart decreases after thyroidectomy.

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COMPLETE HEART BLOCK IN DIPHTHERIA.

By H. M. MARVIN and R. C. BUCKLEY.

(From the Departments of Internal Medicine and Pathology, Yale University School of Medicine, and the New Haven Hospital, New Haven, Conn.)

INVOLVEMENT of the heart has long been regarded as perhaps the most ominous of the grave complications which may arise in the course of diphtheria because of its almost certain fatal ending. Observers differ as to the exact cause and nature of the cardiac involvement, but there seems to be general agreement that changes in the conduction system, as revealed by electrocardiograms, are to be regarded as evidence of myocardial damage and usually presage a fatal issue. The injury to the conduction system may be revealed clinically through the familiar picture of complete dissociation of auricles and ventricles, with slow and regular ventricular rate; more commonly, however, in our experience, the outstanding feature is a gross and complex irregularity of the heart's rhythm which cannot be analysed clinically, and is shown by electrocardiograms to depend upon profound changes in the junctional, sinus and ventricular conduction system. It is important to emphasise at the outset that the records obtained from such patients are highly abnormal and bizarre.

A review of past records has brought to light but few reports of complete heart block in diphtheria. In a condition which is characterised by such complex changes in mechanism and rhythm, we have felt that instrumental records were essential in diagnosis, and have therefore considered as proved cases only those patients from whom electrocardiograms or polygraphic tracings have been obtained. A summary of these will be found in the upper part of Table 1.

In addition to this small group with proof of the disorder, there have been a few cases reported which must be tentatively accepted as instances of heart block because of the clinical picture and slow ventricular rate. Especially convincing is the report of Dunn¹, while that of Averb² almost surely represents a high grade partial block or complete dissociation. The extraordinary case reported by Hellhecker³, in which the ventricular rate during the seizures fell to five per minute, is probably to be regarded as one of complete block, but not to be ascribed with certainty to epithelial damage. White and Smith⁴ publish in their article three charts of fatal

cases, illustrating a fall in heart rate to 20, 25, and 31 respectively, and their clinical description of patients with such low rates corresponds to that of complete heart block as we know it to-day. Harding⁶ in her admirable thesis, gives short accounts of two patients (*Cases* 373 and 711) who possibly had complete block: the details are not sufficient to make the diagnosis certain. A third patient showed the clinical picture of complete dissociation (*Case* 264), and was regarded as such by the author, but it is curious that the venous pulsations in the neck were seemingly at the same rate as the ventricular beating, namely, 32 per minute. Finally, Smith¹⁷ mentions briefly that many of his patients had high-grade heart block, but does not give details of the clinical course or post mortem findings. Several of his published figures show complete dissociation. In another paper he publishes figures illustrating complete block, but these curves were taken after respiration had finally ceased and are ascribable to asphyxiation rather than to specific involvement of the conduction system.

A summary of the recorded cases of 2:1 heart block, and of the probable cases of complete heart block, will be found in the lower part of Table I.

The present report concerns two cases. In both of them it was possible to follow the development of the cardiac changes until death, and in one of them we were able to study the histological picture of the heart and conduction system.

Case 1.

Andrew P., a twelve year old schoolboy, was admitted on December the 15th, with the following history: On December the 10th he had a rather severe headache and vomited once after the evening meal. On the next day he complained that his neck was painful and that it hurt him to swallow. A physician was summoned, who took cultures from the throat and returned five hours later to administer 10,000 units of antitoxin intramuscularly. During the following three days the boy vomited frequently, grew steadily worse until the evening of admission, when his condition appeared so desperate that he was sent to the hospital.

On admission he was quite prostrate. The neck showed a collar of diphtheritic adenitis and oedema: the tonsils were swollen and covered with a greyish pseudo-membrane which extended on to the soft palate. The heart was not enlarged: its sounds were faint everywhere except in a small area just below the nipple, where they could be heard clearly. The rhythm was regular. The radial pulse was barely palpable. The blood pressures were 65 (syst.) and 50 (diast.). No petechiae were to be seen. The white cells numbered 25,800, of which 65 per cent. were polymorphonuclears and 26 per cent. were lymphocytes. The urine showed a trace of albumin and many granular casts.

An electrocardiogram, taken immediately after admission, showed a normal mechanism with moderate tachycardia and very high pointed *P*

TABLE I.

Case No.	Date.	Author.	Age.	Sex.	Duration.	Ventricular rate.	Evidence.	Day of onset.	Termination.
<i>Proved cases of complete heart block in diphtheria.</i>									
1	1910	Magnus-Alsleben ¹¹ ...	8	M	5 days	29-38	Polygram	4th	Death.
2	1910	Fleming and Kennedy ⁴	10	F	3 days	46-54	..	7th	..
3	1911	Price and Mackenzie ¹⁴	9	F	5 days	34-48	..	5th	..
4	1912	Röhmer ¹⁵ (Case 4) ...	8	F	60 hrs.	39-44	ECG	7th	..
5	1915	Parkinson ¹³	22	M	?	62	Polygram and ECG	22nd	Recovery.
6	1920	McCulloch ¹²	8	F	36 hrs.	27-49	ECG	8th	Death.
7		12	F	4 days	35	..	?	..
8		1	F	Few hrs.	66	..	9th	..
9	1921	Schwensen ¹⁶	9	M	1 day	28-30	Polygram	8th	..
<i>Cases of 2:1 heart block.</i>									
1	1914	Hecht ⁷	3	M	4 mos.	50-60	ECG	3rd	Recovery.
2	1914	Hume ¹⁰ (Case 2) ...	7	M	2 days	90	Polygram	12th	Death.
<i>Probable cases of complete heart block.</i>									
1	1888	Huguenin ⁹	19	F	1 day	32		13th	Death.
2	1908	Dunn ³	11	M	3 days	28-40		9th	..
3	1910	Amenomiya ² (Case 6)	17	M	2 days	24-35		7th	..
4	1911	Heilhecker ⁸	14	M	3 days	5		?	Recovery.
5	1912	Röhmer ¹⁵ (Case 2) ...	3	F	?	67		?	Death.
6	1921	Allen ¹	17	F	2 days	22		6th	..
7	1921	Friedmann	17	M	2 days	12-30		7th	..

waves in leads II and III. The conduction time was 0.18 of a second. Immediately after admission, 20,000 units of antitoxin were given intramuscularly. Eight hours after admission, petechial hemorrhages were seen in the skin of the right upper arm and chest. His condition grew rapidly worse during the day, and did not seem to improve after a transfusion of 250 cc. of blood. Electrocardiograms were taken at frequent intervals throughout this day, the sixth of the disease. Eleven hours after admission it was noted (Fig. 1) that the A-V conduction time had lengthened to more than 0.2 of a second, without other appreciable changes from the original record. Twelve hours

later, however, complete heart block was present (Fig. 2), and persisted until death.

On the morning of the 16th, petechial hæmorrhages were seen all over the body, but the general condition seemed to be about the same. Blood pressure was 80/55. There was but little change during the day; electrocardiograms taken at intervals of a few hours showed increasing disturbance of intraventricular conduction (Fig. 3). Late in the evening he suddenly became ashen in colour, respirations became gasping, and the pulse could not be felt at the wrist. The heart sounds were very feeble and irregular for a moment, then ceased.

Comment: It is of interest to note that cardiac involvement occurred in this case despite the early administration of antitoxin. The child was extraordinarily toxic on admission, and the administration of a large dose of antitoxin at that time was without apparent effect. Clinically, the finding of chief interest with regard to the heart was the extreme faintness of the sounds, which were practically inaudible except in a small, sharply localised area near the apex. Perhaps the most unusual feature of the case, however, was the persistence of a rapid ventricular rate in the presence of complete dissociation. Calculations from long strips of film showed the auricular rate to be 110, and the ventricular rate 92 at the time Fig. 2 was recorded. At no time after the onset of complete block did the ventricular rate fall below 80 per minute, and we were never able to elicit any signs by which the condition of heart block could be recognised, even after we were aware of its presence. This but serves to emphasise what we have long felt: that electrocardiograms are essential to the study of diphtheria patients, and it is only after an examination of all records that one can speak with confidence of the disturbed mechanism of the heart.

Case 2.

William P., a boy of sixteen years, was admitted to the hospital on August the 2nd, complaining of difficulty in swallowing and swelling of the neck. He stated that four days previously he had awakened with a sore throat, but it was not severe enough to prevent his going to work. It grew rapidly worse during the day, and he returned home and went to bed, but slept very little that night. The following morning the difficulty in swallowing was more pronounced and the swelling of the neck greatly increased. The condition grew steadily worse, and on the following day a physician diagnosed diphtheria and administered 20,000 units of antitoxin intramuscularly. The patient was then sent to the hospital.

Examination showed a well developed boy with conspicuous œdema of the neck. The breathing was through the mouth and quite noisy, but neither rapid nor laboured. His face was flushed and slightly dusky. The throat showed a dirty grayish white membrane covering both tonsils, the

larynx, pillars, and part of the soft palate, with considerable swelling of the entire throat. The heart was not enlarged, the sounds were regular and of normal quality, the rate was 80 per minute. No murmurs were heard. There was slight cyanosis of the nail-beds.

The patient was given 16,000 units of antitoxin intramuscularly at once. Cultures and direct smears from the throat showed the presence of diphtheria bacilli. White cells numbered 18,500, with 75 per cent. polymorphonuclears. The urine showed a trace of albumin, with a moderate number of granular casts and white blood cells; these abnormalities persisted until death. An electrocardiogram taken on the day of admission showed a normal mechanism (Fig. 4).

The moderate fever present on admission decreased gradually, and the temperature was normal by the sixth day. The membrane in the throat finally became detached and disappeared, and the swelling of the throat subsided within several days. The rhythm of the heart and its sounds remained unchanged until midnight of the fourth day, when the radial pulse was counted at 65 per minute, while the rate four hours previously had been 90. On the following morning it was noted that the rhythm was not entirely regular, and that there was a peculiar variation in the intensity of the first heart sound, which had become faint and muffled. At irregular intervals this sound would become loud and clear. Complete heart block, with occasional simultaneous contraction of atricle and ventricle, was suspected, and an electrocardiogram showed complete dissociation (Fig. 5).

On this day, the ninth of the disease, vomiting first made its appearance, and continued with increasing frequency until death. Apart from vomiting, the chief symptom was abdominal pain, which was present almost constantly. The most notable objective sign was the extreme quietness and lassitude of the patient—a sign which we have learned to expect in practically all patients with diphtherial myocarditis.

There was very little change in the general condition until the day of death, the fifteenth day of the disease. On that morning the patient was quite cyanotic, the extremities were blue and cold, the pulse at the wrist was barely perceptible. The heart rate was quite irregular, and its sounds faint. It was decided to try the effect of atropine. The heart rate and rhythm were noted for about ten minutes, then 1.3 mgm. of atropine sulphate was given subcutaneously, and almost continuous clinical observations and electrocardiograms made until death occurred forty-eight minutes later. Eight minutes after the injection, Cheyne-Stokes respiration appeared and cyanosis became slightly more intense, but the heart showed no significant change. During the ten minutes preceding atropine, the heart rate had varied between 48 and 80, and was constantly irregular; during the three-quarters of an hour of life after atropine, it varied between 56 and 90, and was constantly irregular except for a short period two minutes before death. Forty-eight minutes after the atropine, he said that he felt very ill, and

asked to have his head raised; immediately after speaking he had a short generalised convulsion and, at its conclusion, the heart had stopped beating.

From the time of appearance of heart block until death, electrocardiograms were taken several times a day. They showed (Figs. 6 to 11) a persistence of the complete dissociation until the end, with steadily increasing disturbance of intraventricular conduction as shown by change in the *Q.R.S.* group. The short portions of record here reproduced were selected to show the changes in the ventricular complex from day to day, and therefore do not display the absolute irregularity in rate and rhythm which prevailed during the last four days of life. On many occasions the heart rate changed from forty or fifty per minute to more than a hundred in the brief interval between recording lead *I* and lead *II*, and it was seldom regular for more than thirty or forty seconds.

Autopsy, performed on the day of death, was limited to an abdominal incision, so that an examination of the neck organs and vagus nerves was not possible. The heart alone will be described.

Heart. After removal, the heart was fixed and preserved by a modified Jores-Klotz method and kept intact until there was opportunity for its study. It weighed 250 grammes and was not enlarged. The epicardial surfaces were moist and shining except where multiple haemorrhagic areas of pin-head size were scattered over the posterior surface of the left ventricle and about the apex of the right ventricle. There was but a small amount of subepicardial fat, distributed chiefly about the coronary vessels. The endocardial surfaces were everywhere intact and smooth. The left branch of the A-V bundle was not identified grossly. The valve leaflets, cusps, and chordae tendinae showed no macroscopic changes. The walls of the ventricles seemed normal in thickness. On section, the myocardium was of a uniform reddish-brown colour.

For microscopic examination the following blocks were cut:—(a) A block containing the A-V node, A-V bundle, and beginning of both bundle branches. This was fixed and embedded in its entirety, and 4,200 sections were cut, each ten micra in thickness. Every tenth section from the upper part of the block was mounted and stained with haematoxylin and eosin; after studying these preparations, every section from the area of division of the bundle into its two main branches was mounted and stained with haematoxylin-eosin or Van Gieson's stain. (b) A block containing the sino-auricular node, of which 2,400 sections were cut. Every tenth section was mounted and stained with haematoxylin-eosin. (c) Blocks from both auricles, both ventricles, and from the papillary muscles were fixed and stained as above. Altogether about 700 sections were studied.

The sino-auricular node. The sino-auricular node was readily identified in 220 of the 240 sections studied. It was normal in size and form. In all of the sections a moderate number of small mononuclear cells and a few

polynuclear cells were seen: occasional collections of 30 to 50 small mononuclear cells were seen in the upper portion of the node, sometimes in the nodal tissue and sometimes in the auricular tissue at the periphery of the node. These collections were often perivascular in location. There was a small amount of cellular destruction, evidenced by the finding of nuclear fragments. The blood vessels of the node and the adjacent auricular tissue were distended and very numerous. The muscle fibres contained in the nodal tissue, except for moderate swelling, appeared normal and were well stained.

The A-V node was recognised from its position at the right posterior portion of the central fibrous body, and by the characteristic network of pale-staining, closely grouped, multinucleated fibres. It was followed in section after section as it passed through the fibrous body and was continued as the main bundle in the ventricular muscle of the septum. In many sections there were scattered small mononuclear and eosinophile cells. The ventricular portion of the bundle was more difficult to recognize, but by staining deeper sections it could be identified. In that part of the bundle just anterior to the fibrous body, there was no cellular infiltration, but the tissue was moderately oedematous. Immediately adjacent to this part of the bundle a most extensive infiltration involved the septal musculature of the right ventricle: the process consisted of cellular foci composed of about 95 per cent. small mononuclear and 5 per cent. eosinophile cells, actually replacing areas of cardiac muscle. In addition, a diffuse interstitial infiltration by small mononuclear and eosinophile cells was seen, which increased in degree as the membranous septum was approached. The bundle itself was oedematous and showed moderate infiltration with small mononuclear and eosinophile cells, but as the point of division was approached focal collections, similar to those seen in the adjacent muscle, replaced parts of the bundle fibres and caused a complete interruption. This interruption occurred at the point where the right branch was given off: the origin of the left branch could not be traced. The reaction about the most anterior portion of the bundle at this level, both in and adjacent to the conducting tissue, was very intense.

Cross sections of the *left branch* were studied from the first point at which it could be identified to the areas in which it thinned out and was lost in the focally infiltrated subendocardial tissue of the lower septum. At its uppermost level it was seen to be densely infiltrated with small mononuclear and eosinophile cells and was surrounded by an irregular wall of the same types of cells, which actually replaced the usual muscle fibres. The tissue of the branch was oedematous, and fibres, where they were not replaced by invading cellular elements, were swollen, granular, and poorly stained. As the main portion of the branch descended, the cellular infiltration decreased greatly, but it remained very dense in the adjoining septal musculature. After its division into three smaller branches, it was seen that the smaller anterior divisions were involved, but the posterior one was not. The surrounding subendocardial involvement of the septum, both interstitial and focal,

remained as extensive as in the upper levels, and made any recognition of the left branch in the lower sections impossible. It seems probable that this tissue was entirely replaced by the intense cellular reaction, for nowhere in these lower sections could any fibres of the bundle be identified, while on the opposite side of the septum the right branch was seen in every section. No Purkinje fibres were seen in any portion of the left division, although sections through the septa of other young adult hearts show beautifully the Purkinje fibres in the lower part of the left branch.

The *right branch* was studied in about 300 sections. At its point of origin there was an extensive cellular reaction which interrupted the main bundle and continued into the right branch. In its upper course this branch passed through what appeared to be the most heavily involved portion of the septum. From its beginning, it was surrounded by and was the seat of a severe pathologic process, and the few muscle fibres it contained were swollen, vacuolated, poorly stained, and frequently without nuclei. As the division was followed downward, an increase in the cellular reaction and in the amount of oedema was perceptible. At its lower end this branch approached the endocardium, under which the tissue showed just as dense an infiltration as on the left side of the septum.

Sections from various portions of the *heart muscle* revealed that no area was free from the pathologic process, which varied in degree, being less severe in the auricular tissue than in the ventricles and papillary muscles. In both auricles a moderate interstitial infiltration, largely perivascular, existed. The cells were predominantly small mononuclear in type, but occasional eosinophile and polymorphonuclear cells were seen. The tissue was oedematous. In the right auricular appendage numerous thrombi were enmeshed in the musculi pectinati. Sections of the right and left ventricles presented similar pictures, namely, diffuse interstitial and focal cellular collections. Some of these foci were 0.5 to 1 mm. in diameter and could be seen with the naked eye; examination with the microscope showed that only the shadowy outlines of the cardiac fibres remained. The fibres adjacent to these areas were finely vacuolated, granular, swollen, poorly stained, and sometimes possessed no nuclei. The majority of the larger collections of cells were located just beneath the endocardium of the septum, columnæ carneæ, and papillary muscles. The same type of reaction was seen in the papillary muscles, and was especially severe in the septum; extensive parenchymatous and interstitial damage was noted in every section studied.

The character of the reaction in the various portions of the conduction system and of the myocardium is shown in the accompanying drawings (Figs. 12 and 13).

Comment: In this case, as in the first, it is to be noted that the ventricular rate was frequently rapid despite the presence of complete heart block; on many occasions during the last two days of life the rate was above 100 per minute, although it was usually between 50 and 70 per minute.

Heart block was suspected because of the variation in intensity of the first heart sound; with this exception, there was no definite clinical sign of the condition until the third day after electrocardiograms had revealed its presence. The rate then fell to 36 per minute, and remained at about the rate of 40 for most of one day.

The irregularity in rate and rhythm, which was such a conspicuous feature of the picture, is not shown in the figures, which were selected primarily to illustrate the character of the ventricular complexes. At almost any time within the last three days of life, changes in rate between 40 and 120 per minute during a period of three or four minutes, could be demonstrated and the irregularity in rhythm was so high in grade as to suggest auricular fibrillation.

The profound and progressive changes in the ventricular complexes of the electrocardiogram are clearly shown in Figs. 6 to 11, and require but little discussion. It is of considerable interest to observe, however, that the first abnormal tracing (Fig. 7) indicates not only complete heart block, but also what may be interpreted as disturbed conduction along the right branch of the bundle. There is but one point in the heart at which a single lesion could be situated to produce these two effects, namely, where the right branch is given off from the main bundle. It will be recalled that the only lesion found in the main bundle sufficient to cause complete interruption lay precisely at this point, and was apparently the first significant change in the conduction system. The complete reversal of all ventricular complexes in the following figure (Fig. 8), with a notable increase in their duration, is probably to be interpreted as indicating progressive involvement of the bundle branches, the changes in the left now overshadowing those in the right. To a great extent this indication of predominant damage to the left branch was confirmed by the histologic findings; the lower portion of the left division was apparently completely destroyed, while the right branch, although severely invaded, could be followed in all sections.

Only four of the nine proved cases of complete heart block previously recorded appear to have been submitted to post-mortem examination; these were the patients of Magnus-Alsleben, Fleming and Kennedy, Price and Mackenzie, and Röhmer. In three of them the sino-auricular node is said to have been normal, while in Magnus-Alsleben's case no mention is made of this node. In only one of the four was an acute inflammatory process described (Fleming and Kennedy), and in this it was confined to the *A-V* node and first part of the main bundle. In addition a diffuse and focal lymphocytic reaction in the ventricular muscle and in the auricular tissue near the sino-auricular node occurred. Price and Mackenzie found no changes in the sino-auricular node or the *A-V* conduction system, but noted extreme degeneration of the cardiac muscle, with diffuse and perivascular round-cell infiltration. Magnus-Alsleben found considerable waxy degeneration of the bundle, and extensive old lesions of the endocardium

in the region of the left branch of the bundle. Although Röhmer noted in his case extensive hyaline degeneration near the point of division of the bundle, with considerable round cell infiltration, he did not consider the changes sufficient to have caused complete dissociation. The present case, the fifth reported with its post mortem examination, showed far more severe and extensive changes in the myocardium and in the conduction system than did any of the others.*

SUMMARY.

Two cases of complete heart block in diphtheria are added to the nine proved cases collected from the literature. Electrocardiograms in both instances showed pronounced and progressive changes in the ventricular conduction system.

In both cases the electrocardiogram revealed the presence of heart block before the diagnosis could be made clinically; in one of them the condition would not have been suspected at any time without such records. The ventricular rate was rapid in both patients, and in one was totally irregular for several days before death.

The autopsy in the second case showed extensive changes in the myocardium, with profound damage to the conduction system. There was apparently a close correlation between the electrocardiographic evidence and the anatomic findings.

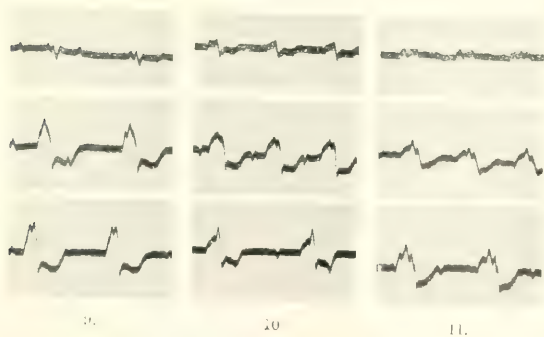
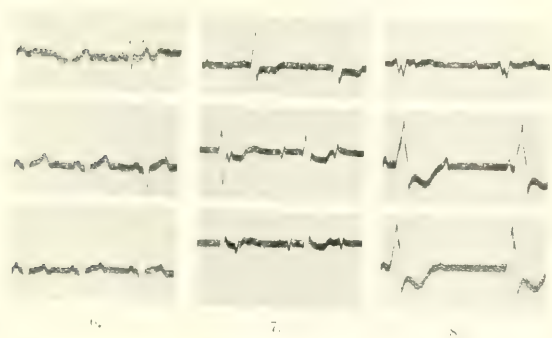
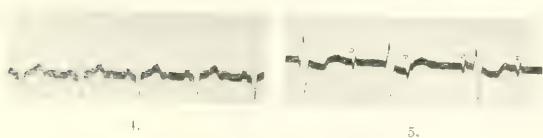
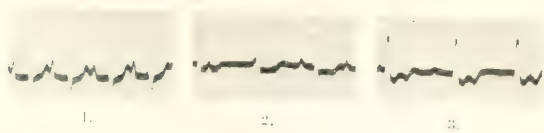
The authors desire to express their thanks to Dr. Edwards A. Park for permission to use the clinical notes of *Case 1*; to Dr. Alfred E. Cohn for his kindness in dissecting the heart of *Case 2*, and to Mr. Hemberger for his beautiful drawings of the microscopic sections.

* Two cases of complete heart block were unintentionally omitted from Table I; those reported by Aviragnet and Soudier (*Archiv. d. malad. d. Cœur*, 1918, XI, 241) and Blacher (*Jahrb. f. Kinderheilk.* 1923, CI, 13). The tracings illustrating 2:1 heart block in the latter paper are too fragmentary to be convincing.

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- Fig. 1. *Case 1.* Taken at noon on sixth day of disease. Lead *II*. Shows partial heart block with delayed conduction. In this and all succeeding electrocardiograms, distances between abscissæ represent 10^{-4} volts, and time is in fifths of a second. Rates have been calculated from long strips of film in all instances.
- Fig. 2. *Case 1.* Lead *II*, taken twelve hours after Fig. 1. Shows complete heart block, with auricular rate of 110 and ventricular rate of 92.
- Fig. 3. *Case 1.* Lead *II*, eleven hours after Fig. 2; seventh day of disease. Auricular rate 88, ventricular rate 80 and moderately irregular.
- Fig. 4. *Case 2.* Lead *II* on admission, fifth day of disease. Normal.
- Fig. 5. *Case 2.* Lead *II* four days after Fig. 4. Complete heart block, with auricular rate of 84 and ventricular rate of 53. There is also defective conduction along the right bundle branch.
- Fig. 6. Same as Fig. 4; three leads of original record for comparison with those following. Normal electrocardiogram.
- Fig. 7. *Case 2.* Three leads taken on eleventh day of disease. Complete heart block with probable partial right bundle branch block.
- Fig. 8. *Case 2.* Three leads on thirteenth day of disease. Note complete reversal of ventricular complexes since Fig. 7. Complete heart block and left bundle branch block.
- Fig. 9. *Case 2.* Three leads on fourteenth day. Complete heart block. Note the increasing disturbance of intraventricular conduction.
- Fig. 10. *Case 2.* Three leads on fifteenth day, before atropine.
- Fig. 11. *Case 2.* Three leads thirty minutes after atropine. Extreme distortion of ventricular complexes. About fifteen minutes before death.



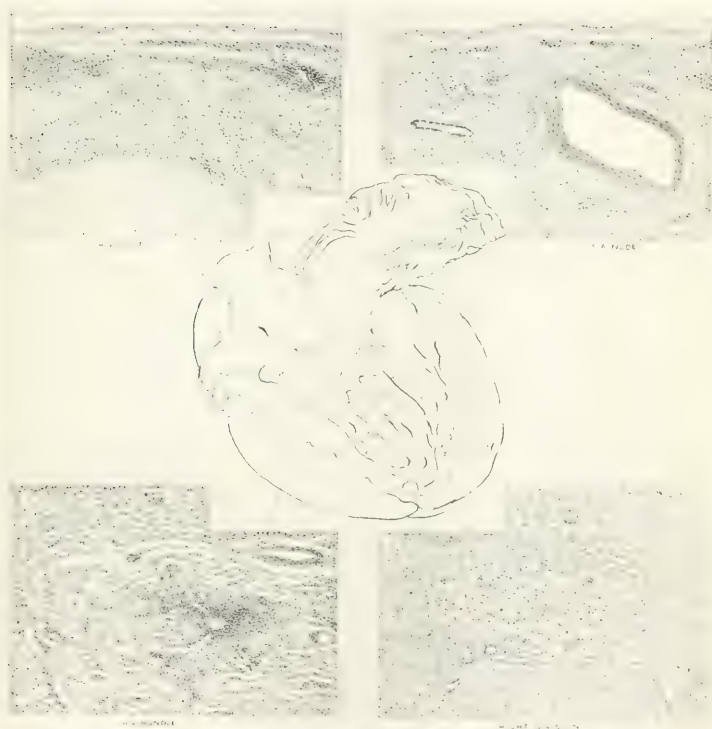


FIG. 1. HEART AND ITS ATTACHMENTS IN THE DIPHTHERIA. A. FALDE, KANNOE, HAN & BROWN. (2000) (2000) (2000) (2000)

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A. FALDE

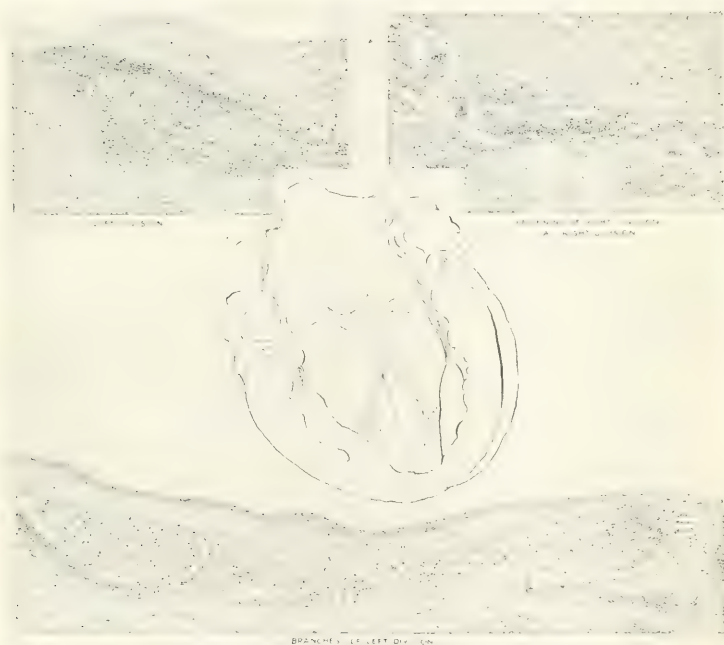


FIGURE 1. ELECTROCARDIOGRAMS OF THE HEART BRANCH (LEFT BRANCH AND RIGHT BRANCH) WITH THE HEART BLOCK.

13

LOCAL CHANGES OF COLOUR IN THE SKIN DEPRIVED OF
ITS NORMAL BLOOD SUPPLY; WITH REMARKS ON
LOCAL ASPHYXIA.*

By Dr. E. P. WOLF (Chicago).

*(From the Cardiographic Department, University College Hospital
Medical School.)*

IN 1898 Bier¹ studied the meaning of the so-called "reactive hyperæmia" which occurs when the circulation of a limb, previously delivered of blood, is restored. He contended that the active dilatation of the blood vessels responsible for this hyperæmia occurs in response to arterial blood entering the limb at the release; and that conversely, the blood vessels contract in response to venous blood. Bier expressed the view that the vessels are in these directions sensitive to the quality of blood lying in them, a sensitivity which he termed "Blutgefühl." Amongst the evidence brought forward was an experiment on the arm; he produced a slight venous congestion in the arm by winding a rubber bandage around its upper part and then abruptly closed the circulation; after a time the limb so treated became uniformly cyanosed; in about 15 minutes white spots appeared on the skin, predominately on the upper arm, but occurring also on the forearm and hand. These white spots were explained as being due to contraction of the vessels in response to their stimulation by venous blood. Recently Carrier and Rehberg³, working under Krogh's² direction, have reinvestigated these spots and have come to different conclusions. These workers believe that in the conditions described by Bier, spots of two colours appear, namely, white and red, the latter having an arterial colour and appearing on the hand before white spots are seen on the arm. The red spots were found to be fairly uniformly distributed, appearing chiefly on the back of the hand and around the base of the thumb; their colour and distribution led Carrier and Rehberg to conclude that the spots are due to fresh arterial blood passing into the arm through collateral channels in the bones of the arm. The white spots seemed to them to be twofold in origin, being in part ascribed to

* Work undertaken on behalf of the Medical Research Council.

feeding of the skin vessels with collateral arterial blood, and in part to a contraction of the vessels in response to cold. Krogh agrees with these conclusions, and points out that the white spots do not appear on a limb maintained in water at 35°C.

The present observations have followed the same lines, and in general confirm Carrier and Rehberg's conclusions.

The method is as follows:—A Riva-Rocci armlet is placed high on the upper arm and is pumped to 30 mm. Hg. for 3 minutes. The veins being now engorged at that pressure, the armlet pressure is abruptly raised to 200 mm. Hg., thus completely obstructing the brachial artery and veins; the arm is now allowed to hang by the side. The events which follow show much variation in detail from subject to subject.

The red spots.

In general these spots appear first, and within 2 or 3 minutes after occlusion. They occur with considerable constancy on the palm of the hand and on the backs of the elongated fingers especially that of the index finger. Occasionally similar spots are quite distinct over the wrist and even on the lower part of the forearm, particularly its ulnar aspect. If these spots are outlined on the skin when they first appear, they are found to spread marginally. They are not of a really bright red colour, though appearing to be so against a blue background; if the latter is covered with white paper, the spots appear bluish and when compared with bright hyperemias produced on the control arm. In repeated observations on the same subject it is found that the red spots appear at much the same localities from hour to hour or day to day; though varying in form in these circumstances, the areas affected are otherwise remarkably constant. The distribution of the red spots, and particularly their reappearance in the same situation day after day, lends distinct support to Carrier and Rehberg's view that they are fed by anastomosing channels which escape compression and obstruction.

If fresh arterial blood reaches these parts of the skin which remain redder while the neighbouring skin becomes blue, it would be anticipated that these red areas would be warmer than the blue. This is found to be the case. Using the thermoelectric couple previously described⁹, readings made in about 100 instances and averaged. The temperature of the various areas of skin, similarly colored, is variable, and in comparing red and blue areas the former may be 0.4°C. cooler or 0.8° warmer than the latter; it is therefore necessary to average many readings. In the average the red spots are 0.22° warmer than the surrounding blue skin (the latter standing at the average value of 25.7°C.).

This average difference of temperature is not great, indicating that if fresh arterial blood reaches the spots the flow is relatively small; the bluish tint in the red coloration suggests either a very slow flow or an admixture with asphyxial blood.

The actual amount of blood going to the forearm when the main vessels of the upper arm are occluded by an anastomosis at high pressure, can be measured plethysmographically. This has been done repeatedly in the subject used most frequently for the remaining observations. The arm has been inserted into a water plethysmograph, maintained at 35°; the arm has been congested and the vessels occluded, as in the preceding observations; subsequently it remains motionless for 10 or 15 minutes, while a volume curve is written. The several observations made under these conditions show that about 16 cc. of blood leaks into 640 cc. of forearm in a period of 10 minutes. The inflow of fresh blood is therefore about 0.025 cc. per minute to each 100 cc. of tissue; this is not uniformly distributed, but may otherwise be compared with the natural flow to the same arm at a similar temperature. This amounts to 6.8 cc. per minute per 100 cc. of tissue.

Now if the view is correct that the red spots are the result of this leakage of fresh blood into the arm by anastomoses in the bone, and the observations previously described point in this direction, it should be possible to prevent them occurring. If the ordinary 12 cm. cuff on the upper arm is replaced by one of 18 cm. width and this is adjusted to cover the whole elbow joint, plethysmographic records for the forearm inscribe straight lines. In these circumstances no blood enters or leaves the arm, and no red spots appear.

It is clear therefore that Carrier and Rehberg are right in concluding that these red spots are attributable to collateral anastomoses. When a blood pressure anastomosis is used in the usual fashion, the channels through the humerus remain uncompressed, and arterial blood, small in amount though it be, passes by way of the bone, re-enters the main arteries of the arm below the cuff, and is slowly carried forward along the radial and ulnar arteries to the wrist and hand, to show in the skin in various places.

The white spots.

These, in general, develop on the occluded arm a little later than the red. The inner surface of the arm and the region of the elbow is sprinkled with many small irregularly shaped white spots, within 5 minutes. These spots have at first a diameter of 2 or 3 mm., they grow in size and coalesce; others appear within 10 minutes and the arm and forearm are eventually covered with irregular white patches, these contrasting vividly with the background of blue skin. By this time also the greater part of the hand presents numerous white areas. From observation to observation, in one and the same individual, they vary in size and appearance. Unlike the red spots, they also vary widely in their distribution, and do not favour precise skin areas as do the former. Any small area of the skin may become blanched, the same or any other area may remain unblanched in given observations; a fact which seems contrary to Carrier and Rehberg's suggestion that collateral feeding plays a part in their formation.

The temperature of about 75 of these blanched areas has been taken. They are found to vary from 0.5° more to 0.65° less than the surrounding skin temperatures, being on the average 0.26° colder than the surrounding skin. The white spots averaged 26.60°C., and the surrounding blue skin 26.86°. This temperature difference, while it is opposed to the view that the white spots are in any way "arterial" spots, is compatible with the view that they may be found as a reaction to cooling. Compression of the elbow by means of a wide cuff, a procedure which, as we have seen, completely prevents blood flow to the arm, has no apparent influence upon the development of white spots. In these circumstances they appear in the same number and have the same distribution and varying forms as when the narrow cuff compresses the upper arm.

Effects of temperature. In room temperatures of from 17–22°C., white spots appearing on the congested arm in which the circulation has been stopped by an armlet placed on the upper arm, are very variable in number and distribution. In some individuals only a few white spots form in 10 minutes, in others the arm is covered with white spots within 2 minutes. Generally speaking, the cooler the room the more numerous are the white spots, and it is noticed that if a draught plays on one surface of the arm, more white spots appear on this than upon a surface which is sheltered. Changing the room temperature in studying these areas of blanching is unsatisfactory, the temperature of the arm varies independently of that of the room. The arm therefore, has been congested and compressed while immersed in water at known temperatures.

If temperatures between 5° and 32° are used, white spots always appear, but they become more numerous and are larger as the temperature scale is descended.

If an arm in which the circulation is at a standstill is immersed in water below 5°, the fingers quickly blanch, and at 0° the blanching extends over the whole hand. Such immersion is painful if long continued; in immersions lasting up to 12 minutes blanching has never extended above the wrist. The skin above the wrist is of a deep blue colour and many white areas pervade it.

If temperatures from 36° to 42° are employed, no white spots appear so long as the arm remains immersed; but if the arm is withdrawn and held in the air, they are seen within one-half to 1 minute.

There is a critical temperature, lying between 33° and 36° for different individuals, above which blanched areas fail to appear; if the water is now cooled 0.5° a few white spots develop. To illustrate one of many observations, when an occluded and cyanosed arm (of E.P.W.) was immersed at 33.4° the colour remained uniformly blue; when the temperature was reduced to 32.8° three small areas of blanching were seen. With further cooling more white spots appeared. Sensitivity to slight change of temperature may be seen in another way. The arm being congested and its main vessels

occluded, half of it is immersed in water at a temperature which just maintains its uniform colouration; the other half is immersed, across a partition, in water 0.5° to 0.6° cooler. Several white spots appear on the cooler half of the arm, and the more the water is cooled the more numerous become the white spots. The reaction to cooling is shown by allowing a stream of colder water to flow down the side of the arm immersed in water at or near 35° C. White spots appear over the arm where the cooler water passes over it, and over that portion only.

These observations confirm those of Carrier and Rehberg and show that the temperature experienced by the arm largely controls the numbers of blanched areas, but it is evident that temperature is not the only factor concerned, otherwise the whole arm should blanch when a critical temperature is passed. At a given moment the vessels in certain areas are ready to respond by contracting when a particular temperature is reached; other areas fail to respond similarly at this temperature and will not respond even though much lower temperatures are experienced. It would, therefore, seem that the skin vessels, involved in this small territory or that, are at a given instant in a very variable condition, some being ready to respond to cold and others not; it also seems clear that this condition of responsiveness or unresponsiveness is changeable from time to time, since the same areas do not respond at a given temperature when the observations are repeated. Since the variability does not depend upon feeding from collateral and guarded vascular channels, it is suggested that it may be determined by the freedom of the circulation to the skin area concerned previous to its occlusion; this, as Ebbecke^{18, 5} has shown, lacks uniformity from area to area, and from one time instant to another. The following observations have been carried out to test this possibility.

In the first class of experiment the circulation is reduced in the arm before the vessels are occluded. This part of the arm is soaked in cold water at 16° for five minutes, the whole is then congested and its brachial vessels are occluded and the entire arm held in water at 33° for five minutes in order to re-warm the skin; it is finally placed in water at 26° for 10-15 minutes; in these circumstances many more white spots appear on that part of the arm which has been soaked previously in the cold water (16° C.) than on that which has not been subjected to cold. A second method which avoids cooling the arm is as follows:—the lower part of the arm is congested for five minutes (venous pressure, 70 mm. Hg.) then the vessels of the upper arm are occluded and the arm held in water at 26° C. for ten minutes; in these circumstances many more white spots appear on the lower half of the arm than upon the upper half.

In the second class of experiment the circulation is increased in the arm before its vessels are occluded. Thus part of the arm is held in hot water (42° C.), the whole arm is congested and its vessels occluded, and the entire arm, after being re-cooled by immersion in water at 33° C. for five minutes, is immersed in water at 26° C.; no white spots appear on the part previously

soaked in hot water, but many white spots appear on the part which has escaped this preliminary treatment. A second method has been used which avoids the preliminary heating: it is as follows:—a part of the arm is rubbed usually a portion of it is freed from the friction, its vessels are then occluded, and the flesh is immersed in water at 26 C.: no white spots appear on the area that has been rubbed, but many white spots are soon seen on the other part of the arm. The results are the same whether the usual cuff is used on the upper arm or a wider cuff is placed over the elbow.

It would seem that anything which decreases the circulation to part of the arm before its vessels are occluded (*i.e.*, applying cold or congesting the limb) causes more white spots to appear. On the other hand, anything which increases the circulation to part of the arm (*i.e.*, applying heat or friction) in the pre-occlusion state, prevents white spots from appearing, or at least leads to many fewer white spots developing. It seems that previous cooling or congestion raises the subsequent critical temperature necessary for the production of white spots and that previous heating or friction lowers it.

The experiments described show clearly that other factors are involved besides skin temperature in the production of white spots on the occluded arm, and support the view that the distribution of the spots is controlled, in some measure at all events, by the local and varying activity of the circulation in the skin. It is, however, impossible to conclude that the two factors, namely, *(a)* previous state of the circulation, and *(b)* the temperature of the skin at the time the white spots appear, are the sole governing factors; for as yet it cannot even be said possible completely to blanch a large area of skin at will. Further factors are possibly involved. The important point to which the observations lead us, however, is this: the explanation offered by Cluett and Reiberg is insufficient completely to account for the appearance of white spots on an arm in which the circulation is at a standstill; Bier's explanation that the vessels concerned contract in response to a content of venous blood is not placed out of court by their observations, although, on the other hand, it still remains unproved. It is still possible that his explanation is in part correct. It is contraction of the capillaries and smaller vessels responsible for the area of blanching; and the present observations, in which it is shown that a previously reduced blood flow favours the subsequent development of blanched areas might be interpreted as supporting the view that the minute vessels, which are responsible for the skin colour, tend to contract in response either to waste products collecting in the blood or in the tissue spaces surrounding them.

Incidentally it may be stated here, that temperature change has comparatively little effect upon the red spots. They appear in the same regions at temperatures varying between 5 and 42 C. When, however, the arm is held in water at 0 and the fingers and hand blanch, red spots previously present vanish in the general pallor.

Independence of nervous control. Changes in skin colour in congested and occluded arms have been investigated in two patients suffering from sensory nerve lesions of several years' duration. One of these patients presented a characteristic paralysis of the muscles and skin supplied by the ulnar nerve, and the other an equally characteristic paralysis of muscle and skin supplied by the median nerve. These cases have been referred to in a previous and recent paper⁸ from this laboratory as instances of nerve degeneration. More than sufficient skin of fingers and hand was affected in these two cases to render them suitable for tests. In both instances, after congesting and occluding the arm vessels, red and white spots appeared on the hand, the sensitive and insensitive skin being equally affected. In both cases the insensitive region had been outlined with ink on the skin, and in both it so happened that single areas of blanching lay in part on sensitive and in part on insensitive skin. In the case of the red spots which, as has been seen, are attributable purely to the distribution of such arterial blood as leaks past the point of occlusion, the failure of nerve degeneration to affect the result is expected. The observation is more important in the instance of the blanched areas since it demonstrated that the reaction is controlled neither by the central nervous system nor by a peripheral nervous mechanism.

Notes on local asphyxia of the hands. The term local asphyxia is here used to indicate a condition of the hands in which they are cold, moist and unusually blue. In the patients who display this condition (sometimes termed acrocyanosis) it is frequent to see relatively bright areas of red skin in a hand otherwise blue, the two colours presenting a vivid contrast. The condition is more conspicuous in cold than in warm weather. It is clear from the colour and temperature of the hands and from the slowness with which the blood returns when it is expressed from the skin, that the circulation in the skin is greatly reduced. The blue areas according to Ekbom⁹ and Parrisius¹⁰ are areas in which the subcapillary venules are dilated; it has been thought that spasm of the deeper veins or of the terminal arteries, or both, may be responsible. Boas² suggests that this condition is due either to constriction of the arterioles or to a marked dilatation of the capillaries. Microscopic examination (Parrisius¹⁰) has shown that the blood flow in the blue areas is more or less at a standstill; in the red areas it is stated to be present. Boas states that the capillaries of the fingers are longer and wider than normal, often show many convolutions and possess a fibrillar wall. Reduction of the blood flow and partial or complete stagnation sufficiently explain the blue colour of the skin. The red areas, which stand out by contrast, are less easily explained since, to the feel, these portions of the skin seem as cold as the rest.

Observations were made on five cases presenting this condition. The hands in these were mottled when they entered a warm room on a cold day; there were well defined blue and red areas scattered over the dorsum and

sides of the hand, and the ends of the fingers were blue and white, although red spots were often present over the phalangeal joints.

In two cases the mottling extended several inches up the arm, to the point where the rolled sleeves reached; above, on the covered arm, the skin was of normal colour. When the temperatures of the red and blue areas were tested, it was found that the red spots were slightly warmer than the blue ones, namely, from 0.1° to 0.8°, and in the average 0.25°. The average temperature of the red areas was 21.58° and the blue 21.33°, temperatures considerably below those of normal hands. The venous pressure in these arms was artificially raised to 30 mm. Hg., and the brachial vessels were then occluded by means of a blood pressure armlet and the hands were watched. On raising the pressure to 30 mm. Hg., some of the red spots increased in size, and upon occluding the brachial vessels they further increased in size, but no new red spots appeared. The difference in temperature between the red and blue spots also increased, namely, from the average of 0.25° to 0.56°, the change was due to a slight rise in temperature of the red spots, while the blue spots were slightly colder. When the elbow was occluded with the broad cuff, no increase in size or temperature of any of the existing spots occurred, but if anything, both decreased, during a period of 10 minutes, and no new red spots were seen. When the unoccluded arm was placed in hot water at 46° C. for 3 minutes and then dried, the hand subsequently maintained a uniform pink colour. The arm was now congested and the vessels occluded, the cuff being placed above the elbow; red spots soon appeared on the hand, and these spots had the same distribution as had those seen originally on the mottled hands earlier in the day. White spots appeared in all of these observations, as in the skin of normal individuals. When the observation was repeated and the vessels around the elbow were occluded, no red spots appeared. These observations indicate that the red areas of local asphyxia are formed in the same way as those which appear in hands which have been artificially congested and from which the greater part of the circulation has been cut off, namely, by arterial blood slowly forcing its way into the red territories along certain selective paths.

CONCLUSIONS.

1. The red spots which appear in the hand after the main vessels of the upper arm have been occluded are due to arterial blood passing through anastomoses in the humerus, re-entering the main vessels of the forearm and passing through these to the hand.

2. White spots occurring over the hand and arm under the same conditions are due in part to a temporary and special responsiveness to cold of the vessels in the given territory affected. Cold tends to produce contraction. Another and important factor influencing the distribution of white spots is previous and local conditions of the circulation. Areas in

which the circulation is relatively reduced at the time of the occlusion, are areas in which the minute vessels of the skin subsequently tend to contract. Bier's original view of the origin of white spots remains neither proved nor disproved, though the evidence as a whole seems to favour the mechanism he suggests as playing a part in their production.

3. In the average, the red spots are warmer than the surrounding cyanosed skin and the white spots are colder.

4. In local cyanosis of the hands, which is spontaneous, it seems that the red areas which are mixed with the blue are due to arterial blood forcing its way slowly into these confined areas. The areas seem to be identical with those which alone receive arterial blood, when the limb is artificially congested and its main vessels are occluded.

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EXPERIMENTAL STUDIES IN ARTERIO-VENOUS FISTULÆ: CARDIAC OUTPUT.

By TINSLEY R. HARRISON, WILLIAM DOCK, and EMILE HOLMAN.

*(From the Medical Service of the Peter Bent Brigham Hospital, Boston,
and the Surgical Laboratory of the Medical School of Harvard University.)*

PREVIOUS analyses of the factors producing changes in the general circulation in the presence of arterio-venous fistulæ have led to conflicting views as to the rôle played by variations in the cardiac output. From the purely hydraulic and mechanical points of view, the introduction of a fistula between artery and vein should increase the rate of flow through that part of the circulatory system involved, namely, through the heart-artery-fistula-vein circuit. Lewis and Drury demonstrated in certain cases of arterio-venous anastomosis that the flow through the arms and skin^{1 and 5} was decreased in the presence of an open femoral fistula and that venous pressure was not raised: and that in animal experiments, in which fistulæ of certain sizes were established for seconds or minutes⁶, neither a general rise of venous pressure nor consistent and demonstrable rise in cardiac output occurred. Their thesis is that in arterio-venous anastomosis of these types the leak of blood directly from artery to vein lowers mean arterial pressure, and that less blood consequently flows out through the capillaries, in its extent compensating for the extra amount thrown directly from artery to vein. In these circumstances they believe that the total effects of the leak in raising venous pressure and cardiac output may be inappreciable or absent: and that cardiac enlargement, occurring in these conditions is due to deficient blood supply to the coronary vessels. They also showed that when the anastomoses are larger, rises both of venous pressure and cardiac output occur. Since these observations were made, additional experimental studies² of the effects of arterio-venous aneurisms on the circulation have emphasised the importance of the size and duration of the fistulæ in determining the extent of the changes in the general circulation. These studies have further indicated that the changes are dependent upon the factors normally concerned in the maintenance of an adequate and uniform blood-pressure. In experiments designed to simulate as closely as possible clinical conditions, significant increases in total blood-volume and pulse rate

were found. In the presence of large fistulae, hypertrophy and dilatation of the heart invariably occurred. It was believed that these changes in the heart were the result of the increased blood flow through the heart per unit of time, and an increased cardiac output was postulated as an inevitable accompaniment of an arterio-venous fistula of large size and sufficient duration. Experimental evidence of such an increase is now presented. Our studies were made on the volume flow through the lungs of dogs in whom arterio-venous fistulae, comparable in size and duration with those found in clinical cases, had been established.

Experimental data.

The volume-flow of blood was calculated by the Fick method, using the minute utilisation of oxygen divided by the difference in oxygen content per cubic centimetre of arterial and venous blood to give the rate of blood-flow per minute through the lungs. The rate of flow through the heart is under normal conditions the same as through the lungs.

The Benedict type of spirometer was used to measure the oxygen utilisation, with the usual tests for tightness of the mask. Blood oxygen content was estimated by the Van Slyke method. Blood was obtained from the ventricles of the heart by puncture through the chest wall. Arterial blood was obtained from the femoral artery. During the determinations the animals were breathing pure oxygen, and we found agreement between the oxygen capacity of the blood and the arterial oxygen content within the limits of experimental error (0.2 vol. %). In many of the determinations, therefore, no attempt was made to use arterial blood, the oxygen capacity of the venous blood being substituted. Care was taken to aspirate the samples only while the respiratory curves were normal and with the needle held in one place so as to avoid obtaining mixed arterial and venous blood. If there was any struggling during the withdrawal of blood it was shown by the spirometer record, and the sample discarded. The oxygen utilisation used in the calculation was that shown by a six-minute period recorded while the blood was obtained. The analyses were made in duplicate, the calculations and readings checked by two observers. Morphine was given to decrease restlessness, but the oxygen utilization was higher and more variable than under basal conditions in dogs trained to the mask. Otherwise the conditions were uniform and normal, permitting comparable observations.

The experiments were identical in all four dogs. The fistula in each case was established under aseptic conditions by suturing together the artery and vein along longitudinal slits of varying length. Healing per primam occurred after each operation.

In every case there was a continuous purring thrill with systolic intensification, accompanied by a loud bruit in the region of the fistula. Following the formation of the fistula there developed a conspicuous oedema of the right hind leg, together with an increased prominence of the superficial

TABLE I.

The volume-flow of blood through the lungs of dogs.

1. *Before the establishment of an arteriovenous fistula.* 2. *In the presence of the fistula.*
 3. *After the elimination of the fistula.*

Dog No.	Date.	Oxygen absorbed per min.	Difference in oxygen content per cem. of arterial and venous blood.	Volume flow per min.		Pulse.	Systolic output per 100 gm.
				Total.	Per 100 gm.		
L12	5 25	197 cem.	0.041 cem.	4807 cem.	36.7 cem.		
	5 30	190	0.040	4750	36.5		
	On the same day, with the fistula occluded by pressure.						
	6 9	190	0.063	3017	23.2		
	6 10	189	0.092	2055	15.8		
	6 22	151	0.068	2220	17.1		
Right femoral fistula, of 15 months' duration, eliminate d.							
L30	5 27	411 cem.	0.072 cem.	5719 cem.	22.8 cem.		(Two hours after feeding)
	5 29	211	0.047	4490	18.0		
	6 2	Right femoral fistula established.					
	6 4	227	0.027	8406	33.6	80	0.35 cem.
	6 22	203	0.029	7000	28.0	96	0.35
	6 24	195	0.023	8478	34.0		
	6 24	Fistula excised.					
	6 26	221	0.061	3634	14.5	72	0.20
L32	6 28	219	0.049	4480	18.0	74	0.24
	5 28	166	0.049 cem.	3388 cem.	22.6 cem.		
	5 30	145	0.056	2589	17.3		
	6 4	Right femoral fistula established.					
	6 12	156	0.040	4750	31.6	83	0.38 cem.
	6 22	184	0.032	5750	38.3	86	0.44
	6 25	156	0.037	4315	28.8	74	0.38
	On the same day, fistula occluded by pressure.						
L33	6 26	156	0.053	2945	10.6	62	0.31
	6 26	Fistula excised.					
	6 27	136	0.050	2720	18.5	66	0.28
	6 29	132	0.060	2200	14.6	66	0.22
	6 4	194	0.080 cem.	2425 cem.	18.7 cem.		
L33	6 10	Right iliac fistula established.					
	6 19	156	0.032	4886	37.5	88	0.42 cem.
	6 24	142	0.031	4580	35.2	92	0.37
	6 26	Fistula ligated.					
	6 27	152	0.064	2720	17.5	78	0.22

veins in the region about the right groin, an invariable accompaniment of a fistula large enough to short-circuit much blood. All the dogs showed a slowing of the pulse on compression of the fistula.

The following protocols illustrate our results and explain the arrangement of the table (Table I).

Dog L12. Weight 13 kgm.. A medium-sized fistula between the right common femoral vessels had been established in March, 1923. In June, 1924, the volume flow of blood through the lungs was measured twice and found to be 36.7 and 36.5 cem. per 100 gm. body weight per minute. With

the fistula obliterated by digital compression the volume flow was reduced to 23.2 ccm. per 100 gm. per minute. On June the 9th, 1924, the fistula was eliminated from the circulation by ligation of the artery and vein proximal and distal to the opening. Following this ligation the volume flow was determined on two occasions as being 15.8 and 17.1 ccm. per 100 gm. per minute.

Dog L30. Weight 25 kgm.. The volume flow was measured on two occasions before establishing a fistula 2 cm. long between the right common femoral vessels, on June the 2nd, 1924. The fistula was excised on June the 24th. The remaining details are included in the table.

Dog L32. Weight 15 kgm.. A femoral fistula 2.4 cm. long was established on June the 4th and excised on June the 26th.

Dog L33. Weight 13 kgm.. A fistula 1.8 cm. long was established between the right common iliac vessels on June the 10th and eliminated by ligation of the vessels both proximal and distal to the fistula on June the 26th.

The volume flow determinations are recorded in Table I. In three dogs before the introduction of a fistula the average flow through the lungs per minute per 100 gm. body weight was 19.9 ccm.. In the presence of a fistula the average flow was 34.0 ccm.. Ten determinations were made including those on *Dog L12* with a fistula of 15 months' duration. After the ligation of the fistula in each case, the average flow fell to 16.6 ccm.. The average systolic output per 100 gm. of body weight was 0.38 ccm. with the fistula present, 0.23 ccm. with the fistula absent.

COMMENT.

It is evident from a study of the table that the introduction of a large permanent arterio-venous fistula into the circulatory system may result in a marked increase in the volume-flow through the lungs and therefore through the heart. We find that in dogs with lesions varying in duration from one day to fifteen months, the cardiac output is almost doubled as the result of short-circuiting a large amount of blood through an abnormal communication between artery and vein. The elimination of such fistulae reduced the minute volume flow to 48 per cent. of that with the fistulae open. Only a small part of this decrease is explained by the slowing of the pulse which accompanies occlusion of the opening between artery and vein. The average systolic output decreased to 60 per cent. of the values found when the fistulae were open.

The increased volume flow and systolic output thus demonstrated indicate a great increase in cardiac effort in the presence of these arterio-venous fistulae. If one accepts the observations of Küllbs³ showing a 50 per cent. increase in the heart weight of young dogs due to exercise, the increased cardiac effort resulting from a fistula is also sufficient to produce cardiac hypertrophy.

SUMMARY.

The volume flow of blood through the lungs of dogs has been calculated from the arterial and venous oxygen content and the oxygen utilization on different occasions over a period of several weeks during which time femoral or iliac arterio-venous fistulae were established and later eliminated.

The volume flow was uniformly increased, by approximately 100 per cent. in the presence of a fistula as compared with the flow prior to the production or following the elimination of the fistula. The increased cardiac effort necessary to propel forward this increased flow was sufficient to cause cardiac hypertrophy in these animals: and the cardiac dilatation, which is frequently though not invariably, associated, may also be explained on the basis of the increased blood volume flow through the heart per minute of time.

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THE ABSORPTION OF FLUID IN CARDIAC DROPSY.*

By CHARLES BOLTON.

*(From the Graham Research Laboratories, University College Hospital
Medical School, London.)*

THE experiments described below form the continuation of a series, which have been published from time to time^{1, 2, 3, 4}, and which were initiated in order to study the succession of events which occurs in uncompensated heart disease.

It is perhaps universally considered at the present time that, although increased output of lymph is the chief factor concerned in the production of cardiac dropsy, nevertheless delayed absorption of fluid plays an important part in assisting the development of this condition. All the published work that I can find relating to this subject deals with absorption from the connective tissue spaces, and apparently no observations have been made relative to the serous cavities. The mechanism of absorption from the serous cavities is, however, fundamentally different from that from the connective tissue spaces and, therefore, the two processes must be considered quite separately. The present series of experiments deals with absorption from the peritoneal cavity only, leaving the other serous cavities and the connective tissue spaces to be dealt with later.

The reader is referred to the communications mentioned above for an account of the details of the various methods which I have employed for the production of uncompensated heart disease in the cat, and of the chain of events which results therefrom. It is sufficient for the purposes of this paper to state that the method selected for these experiments was that of partial obstruction of the inferior vena cava above the diaphragm, because I had previously found that this method produces, in the parts below the point of obstruction, results precisely similar in kind, and only varying in

* The expenses of this research have been defrayed by a grant from the Graham Fund, University of London.

degree, to those resulting from the other methods employed, namely, constriction of the pericardium or simultaneous obstruction of the superior and inferior venæ cavae as they enter the heart. It is also more rapidly and easily performed and the degree of obstruction can be more or less accurately gauged. In all the experiments cats were used. Whatever method be employed for interfering with the diastolic filling of the heart, the effects below the diaphragm are enlargement of the liver and congestion of the portal area, with the development of ascites and commonly œdema of the retroperitoneal tissue, which rarely extends out of the abdomen down the thighs and on to the undersurface of the abdominal wall. In the human subject the effects of gravity are evidenced by œdema of the legs. The blood gradually increases in volume after the first few days with a resulting increase in the dropsy. The other changes do not call for mention here.

From theoretical considerations I had already formed the conclusion that absorption from the peritoneum of the ascitic cat must be occurring at least at the normal rate. At that time I considered the thoracic duct to be the main channel for lymph absorption from the peritoneal cavity, but from certain experiments which I have recently published I was able to show that this is not the case². The part played by the thoracic duct in draining the peritoneum is a subsidiary one. Fluid from the peritoneum passes into the thoracic duct very slowly and in quite a moderate degree. The chief path of lymph absorption is through the diaphragmatic lymphatics to the sternal and anterior mediastinal glands and thence to the right lymphatic duct. Absorption through these channels occurs rapidly and the bulk of the fluid absorbed passes in this direction. The forces giving rise to the flow of lymph are derived from the movements of the diaphragm and the negative pressure in the chest. Von Recklinghausen¹⁰ was the first observer to demonstrate this path of absorption, and references to later work will be found in the paper mentioned above⁵.

I have, therefore, reconsidered the whole question of the absorption of ascitic fluid in the dropsical animal. Experiments bearing on this point which have been already published will be briefly referred to.

Absorption in the normal animal.

In experiments dealing with absorption by the lymphatics it is essential to avoid using dyes which diffuse into the blood through the capillary wall, because, if such dyes are used, the lymph passing out of the capillaries will be already stained and the result vitiated. I found that colloid silver does not diffuse into the blood, as it is unable to pass through the capillary wall

against the blood pressure, and is entirely absorbed by the lymphatics. It is, therefore, a suitable substance, and has been employed in my previous experiments and also in the present series. In a strength of one or two per cent. it forms a black solution which on dilution becomes canary yellow. It stains the lymphatics brown, the glands in their path brown or black, and the lymph in the lymphatics and thoracic duct yellow. In a previous paper⁵ I found that after placing a two per cent. solution in the peritoneal cavity the anterior mediastinal glands and the lymphatics connected with them were stained dark brown in about five minutes and the glands were black in a quarter of an hour. The anterior lumbar gland lying on the cisterna chyli showed staining in half an hour and the lymph in the cisterna became a very definite yellow colour in about an hour. In these experiments the cats were anaesthetised, breathing normally, and lying in the supine position. The lymph flowing from a cannula connected with the thoracic duct in the neck was stained yellow in an hour and thirty or forty minutes. Artificial respiration was employed in such experiments, because in inserting the cannula the apex of the pleura was generally opened by accident. Absorption is slower with artificial than with normal respiration, and quickest in the condition of partial asphyxia and proportional to the violence of the respiratory movements. It is impossible to obtain more exact figures than the above, owing no doubt to individual variations in the animals and to the difficulty in detecting the exact time at which a yellow tint is first to be observed. The figures are, however, sufficiently accurate for the purpose in hand.

Absorption in the ascitic animal.

In these experiments the cats were anaesthetised with ether and placed in the supine position. The respiration was normal. In all cases the abdomen was opened and the amount of ascitic fluid present approximately judged. A solution of colloid silver in normal salt solution was then run into the peritoneum, the strength and the amount of the solution being adjusted so that the resulting mixture of ascitic fluid and salt solution contained as nearly as possible two per cent. colloid silver. After the experiment was finished the animal was killed by bleeding; the amount of peritoneal fluid was measured and the percentage of colloid silver calculated, so as to make sure that the fluid was sufficiently deeply stained, and also to determine approximately the original amount of ascitic fluid. A complete post-mortem examination was then performed, the lymph being extracted from the cisterna by means of a fine glass pipette.

The following table gives the results of these experiments, which are arranged in groups according to the time allowed for absorption.

Cat.	Time since obstruction of vena cava.	* Original amount of ascitic fluid.	Lymph glands.		Cisterna.
			Anterior mediast.	Anterior lumbar.	
Group I.—Killed in $\frac{1}{4}$ ho'ur.					
1	15 days	47 cc.	Almost black	nil	nil
Group II.—Killed in $\frac{1}{2}$ hour.					
2	4 days	10 cc.	Black	Yellow	Yellow
3	14 ..	48	? Faint yellow
4	16 ..	80
5	16 ..	35	Brown
6	34 ..	25	Faint yellow
7	42 ..	50	Yellow
Group III.—Killed in 1 hour.					
8	7 days	25 cc.	Black	Brown	Yellow
9	13 ..	240
10	21 ..	86	Light yellow
Group IV.—Killed in $1\frac{1}{2}$ hours.					
11	20 days	40 cc.	Black	Brown	Yellow

* *i.e.*, The amount finally measured, less the amount of fluid introduced.

It is quite clear from these experiments that there is no delay in the staining of the anterior mediastinal glands, nor of the lymph in the cisterna chyli. There is therefore no delay in the absorption of the ascitic fluid by the lymphatics. In *Cats* 2, 6 and 7 the lymph in the cisterna was definitely yellow in half an hour, distinctly quicker than in the average normal animal. It was not possible to determine whether the anterior mediastinal glands were also stained quicker, because in the normal animal they are stained in five minutes. Whether this was due to slight exaggeration of the respiratory movements I was unable to determine, but it is certain that the dyspnœa of heart disease distinctly aids absorption from the peritoneum. At all events whether or not one is to conclude that absorption is slightly quicker than normal in these animals, there is clearly no delay in the process.

The next experiment proves that the lymph flowing from the thoracic duct is coloured in the same time in the ascitic animal as in the normal, when artificial respiration is employed.

The cat weighed 3,500 grms. The inferior vena cava had been constricted 120 days previously. Ether and artificial respiration were employed in the dorsal decubitus. Canulæ were placed in the thoracic duct and peritoneum at 3.5 p.m. The lymph flow was measured till 3.15 p.m. and at this moment

50 cc. of 3 per cent. colloid silver in 0.9 per cent. saline, were allowed to flow into the peritoneum.

Lymph flow, thoracic duct.		Amount.	Colour.
Time.			
3.5 p.m. to 3.15 p.m.		10.0 cc.	Colourless
3.15 .. 3.25 ..		7.0
3.25 .. 3.35 ..		6.0
3.35 .. 3.45 ..		5.0
3.45 .. 3.55 ..		3.5
3.55 .. 4.5 ..		2.5
4.5 .. 4.15 ..		2.5
4.15 .. 4.25 ..		2.0
Tube changed owing to clotting			
4.40 p.m. to 4.50 p.m.		1.0 .. (approx.)	..
4.50 .. 5.0 ..		1.5 ..	Very faint yellow
5.0 .. 5.10 ..		1.5 ..	Definite yellow

The animal was killed by bleeding at 5.15 p.m. After standing twenty-four hours the blood serum was found to be unstained. The peritoneal cavity contained 105 cc. fluid, so that the percentage of colloid silver in it was about 1.5, and about 50 cc. ascitic fluid had been present originally. By how much the quantity of peritoneal fluid had altered, if it had altered at all, during the experiment it is impossible to say, but it is a matter of little importance from our point of view. The anterior mediastinal glands were stained black, the anterior lumbar gland brown, and the lymph in the cisterna chyli was yellow and of a deeper colour than that flowing from the thoracic duct. The lymph was stained in one hour and forty-five minutes, a period of time within the normal limits. The lymph flow was increased and notwithstanding this fact the lymph was not coloured more rapidly by the ascitic fluid than in the case of the normal animal. The conclusion is that the increased lymph flow through the thoracic duct is not due to increased rate of absorption from the peritoneal cavity. The mere presence of fluid in this cavity will not increase the lymph flow, even if the fluid is under considerable pressure⁵.

A study of the lymph flow in the thoracic duct in the ascitic animal is of interest because it demonstrates (1) that there is no demonstrable increase in the flow during the first few days after the vena cava has been constricted although ascites is present, and (2) that after this initial period the flow is definitely increased and that this increase is not dependent on the amount of ascitic fluid present.

The next series of experiments demonstrates that the lymph flow in the ascitic animal is increased after the first few days as compared with that of the normal animal.

Lymph flow in normal cats.

Cat.		cc. at 10 min. intervals.						cc. first $\frac{1}{2}$ hour.
1	0.8	0.7	0.3	0.5	0.5	0.7		1.8
2	2.0	1.3	1.0	1.0	1.0	0.8		4.3
3	2.4	2.3	2.0	1.4	1.0	0.8		6.7
4	1.3	1.0	0.5	0.6	1.0	1.0		2.8
5	1.7	1.0	0.9	1.0	0.8	1.0		3.6
6	1.1	1.0	1.7	1.0	1.1	0.6		4.1

Lymph flow in ascitic cats.

Cat.		Duration of dropsy.	Ascites.	cc. at 10 min. intervals.						cc. first $\frac{1}{2}$ hour.
1	5	hours	11 cc.	2.2	1.8	1.5	1.2	1.0		5.5
2	24	"	27 "	0.6	0.5	0.5	0.4	0.3	0.5	1.6
3	24	"	20 "	0.8	1.0	0.8	0.5	0.4	0.5	2.6
4	4	days	10 "	1.3	1.0	1.1	1.0	0.8	0.7	3.4
5	2	weeks	21 "	4.2	4.6	3.6	3.0	3.6	3.5	12.4
6	2	weeks 6 days	52 "	5.0	2.9	2.8	2.8			10.7
7	5	"	12 "	5.1	3.2	2.6	2.4	2.0	2.1	10.0
8	5	" 6 "	3 "	4.5	3.0	4.2	3.7	5.4	5.7	11.7
9	7	" 1 "	4 "	4.0	3.5	2.5	2.5			10.0
10	8	" 1 "	7 "	5.5+	8.0	4.5				18.0+
11	10	" 1 "	7 "	5.5	3.7	2.7	2.3			11.9
12	17	" 1 "	55 "	7.0	6.0	5.0	3.5	2.5	2.0	18.0
13	24	" 3 "	40 "	3.2	2.3	0.7	1.3			6.2+

The ascitic fluid, amounting to 31 cc., was removed from the last cat (No. 13) twenty four hours before the lymph flow was estimated; 40 cc. had reaccumulated during this twenty-four hours.

The lymph flow in *Cats* 1 to 4 is within normal limits; in the rest it is definitely increased with the exception of *Cat* 13. The reason for this is that the experiment was made of removing all the ascitic fluid from *Cat* 13 the day before the lymph flow was estimated. It had reaccumulated to the amount of 40 cc., which had depleted the blood considerably. The cat weighed 3.230 grms., so that its normal blood volume should be about 130 cc.. An increase of 40 cc. in such an animal would be about the amount which would be expected from the estimations I have made. The small lymph flow is due to the reduction in its blood volume. It seems perfectly clear that the increased lymph flow in the thoracic duct is in no way indicative of increased rate of absorption from the peritoneal cavity, for the flow is unrelated to the amount of fluid present in the peritoneal cavity, but is related to the blood volume. This view has been already expressed, although direct proof of it was

not forthcoming at the time. It was strongly suggested in the case of a dog with cardiac dropsy and plethora investigated by Starling and myself, in which the lymph flow was increased and in which this increase persisted for a certain time after tapping the abdomen⁶. I was able to demonstrate that in ascitic cats with constriction of the inferior vena cava the blood volume gradually increases and that coincident with, and dependent upon it, there was a rise of venous pressure in the portal and systemic systems behind the obstruction, comparable to that seen when the inferior vena cava is completely ligatured³. A few days elapse after the constriction is applied before the plethora can be demonstrated, and at this time the venous pressures are only moderately raised and sometimes are within normal limits, and the lymph flow in the thoracic duct is normal. As the blood volume increases the percentages of red blood corpuscles and hæmoglobin fall, to rise again as the production of corpuscles increases. There can be no doubt that the increased lymph flow results from the plethora and is thus an index of increased lymph production. It has been known for many years that plethora increases the lymph flow, and that the excess of blood chiefly collects in the abdominal organs⁸. Starling showed that in artificial plethora the excess of lymph comes chiefly from the intestine and liver, contrasting in this respect with complete ligature of the inferior vena cava, the increased lymph production in which condition he showed to occur entirely in the liver⁹. That such an increased outputting of lymph is constant during the whole period of the ascites is quite clear from the fact that, if the ascitic fluid is removed at any period, it reaccumulates within the next twenty four hours, the amount of such reaccumulation depending upon the activity of lymph production. This constant outflow of lymph into the peritoneal cavity I have already demonstrated, and reference to it here necessitates a short consideration of the part played by the blood vessels in absorption.

Absorption by the blood vessels.

The difference between the absorption of ascitic fluid and of salt solution by the normal animal lies in the fact that the ascitic fluid is absorbed as a whole by the lymphatics and at an almost uniform rate. Salt solution is absorbed by the blood capillaries by osmosis and diffusion⁷, the rate of absorption being rapid in the initial stages but falling off during the process owing to the accumulation of protein and various salts in it, so that the force tending to osmosis diminishes, and finally, when osmotic equilibrium is established, the residual fluid is entirely absorbed by the lymphatics. The ascitic fluid in the peritoneum is in osmotic equilibrium with the blood in the capillaries, and, as I have said, is absorbed as a whole at a uniform rate by the lymphatics. If the ascitic fluid of a dropsical animal be removed and replaced by salt solution, the amount of this solution absorbed by osmosis is the same during the first hour as in the normal animal, but the rate of

absorption falls off much more rapidly in the former than in the latter case, and an estimation of the amount of total solids in the introduced fluid shows that this falling off is due to the more rapid accumulation of protein and salts in it. The amount of total solids in this fluid soon equals that in the original ascitic fluid, when osmotic absorption ceases, and the animal is left in practically the same condition with regard to amount and composition of its ascitic fluid as it was at the beginning. The blood vessels thus regulate the composition of the ascitic fluid. The actual figures observed in two experiments were as follows⁵ :—

Absorption of 0.9 per cent. salt solution normal cats.

Introduced.	Solids per cent.	Time in hours.	Remaining.	Solids per cent.	Absorbed.
50 cc.	0.9	1	32 cc.	1.2	18 cc.
70 „	0.9	8	3 „	4.7	67 „

Absorption of 0.9 per cent. salt solution ascitic cats.

Ascites removed.	Solids per cent.	Salt introduced	Time in hours.	Remaining.	Solids per cent.	Absorbed.
11 cc.		50 cc.	1½	31 cc.	2.7	19 cc.
45 „	7.9	70 „	8	45 „	6.6	25 „

The amounts absorbed in the first hour are the same in each case, but the amount of total solids in the remaining fluid in the ascitic cat is double that in the normal cat. After eight hours the normal cat has absorbed almost the whole of its fluid, but 45 cc. remain in the peritoneum of the ascitic cat and the fluid contained 6.6 per cent. total solids, owing to the rapid output of lymph into this cavity. The average amount of total solids in the ascitic fluid of these cats is 6.3 per cent.; 7.9 per cent. is very high. Absorption by the peritoneal blood vessels of the dropsical cat is thus as efficiently conducted as in the normal animal, but in the case of the peritoneum it does not follow that the vascular area, in which increased output is occurring, absorbs the fluid, because there are two sets of vessels concerned (1) those of the portal area which are rapidly producing an excess of lymph; (2) those of the remaining peritoneum which are probably producing no excess of lymph: it may be that the vessels of this area are those chiefly or solely concerned in absorbing the fluid. This point remains to be elucidated.

CONCLUSIONS.

1. Absorption by the lymphatics of the peritoneum is unimpaired in obstructive ascites. The only condition in which it may be supposed to play a part as a factor in the dropsy of uncompensated heart disease is that in which a very high venous pressure at the root of the neck may impede the entrance of lymph into the venous system. This is by no means invariably the case in animal experiments before plethora is established, and in the dog with cardiac ascites referred to above the venous pressure in the jugular vein was 30-45 mm. NaSO_4 (normal = 28-38 mm. NaSO_4 , the increase being $\frac{1}{6}$ - $\frac{1}{2}$ mm. Hg. only).

2. The ascitic fluid is continually being absorbed, chiefly by the lymphatics of the diaphragm and so up through the chest, and to a less extent by the thoracic duct.

3. The presence of the ascitic fluid is due to a continual output of lymph at a rate considerably above the normal. An increase in the amount is due to an increasing output, and a decrease in the amount, leading to final disappearance, is due to a gradual decrease in the output of lymph. The fluid is constantly circulating from the blood to the peritoneum and back again. 5

In a patient with cardiac dropsy the effect of gravity is to relieve the portal system at the expense of the legs. In the horizontal position œdema of the legs diminishes and ascites increases. With the legs down lymph-output into them increases and the output into the peritoneum consequently falls, and, absorption from this cavity continuing, the ascites diminishes.

4. Absorption by the blood vessels of the peritoneum is unimpaired in this form of ascites, but the particular system of vessels concerned in this act is not decided by these experiments.

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OBSERVATIONS UPON THE VASCULAR REACTIONS IN MAN
IN RESPONSE TO INFUNDIN, WITH SPECIAL REFERENCE
TO THE BEHAVIOUR OF THE CAPILLARIES AND VENULES.*

By BENJAMIN SACKS, of New York.

(*From the Cardiac Department, University College Hospital Medical School.*)

THESE studies were undertaken to investigate more fully than hitherto has been attempted the vascular reactions of normal human beings to clinical doses of pituitary extracts.

The subjects were young healthy adults, and all observations, except where otherwise stated, were undertaken with the patient lying supine and comfortably. Blood pressure determinations were made by the auscultatory method. The pulse and respiratory rates were recorded graphically. With the sphygmomanometer armlet, pulse and respiratory receivers adjusted, the subject lay resting for 20-30 minutes or longer as a preliminary to all observations. In instances in which plethysmographic observations on a lower limb were being made the simultaneous blood pressure readings were taken in the semi-recumbent posture. Infundin† was used throughout these experiments for both intravenous and subcutaneous injection. Intravenous injections were made into a vein of the forearm, the dosage employed being $\frac{1}{10}$ — $\frac{1}{20}$ cc. diluted with 3 cc. Locke's solution. For subcutaneous use $\frac{1}{2}$ cc. or 1 cc. diluted with 2 cc. of Locke's solution was injected into the upper arm. When intravenous injections were used a series of uniform readings was first obtained, the needle attached to the syringe was driven into the vein and allowed to remain there until any disturbance arising from the needle prick had subsided. Consequently in none of the readings recorded does this needle prick enter as a causative factor. The moment of injection was usually unknown to the subject. After the injection (intravenous or subcutaneous) observations were continued for 20-60 minutes or longer. Details of other methods are given later.

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† Burroughs Wellcome & Co.'s preparation (original strength, 17 per cent. extract).

TABLE 1. — *Indurans injections.*

Name and dose.	Blood pressure, etc., before and after injection.						Pallor.	Subjective symptoms.
	1 c.c.	1 min.	3 min.	5 min.	10 min.	20 min.	Max. at	
1. P. C. 23	120 B. P. 103 72	110 82	110 82	106 80	104 72	103 70	3 min.	Onset 58 sec. In- crease at end of 30 min. Involves face, neck, hands and forearms.
2. C. R. 33	130 B. P. 120 74	126 90	124 84	121 74	120 74		1 min.	Onset 65 sec. Less 13 min. Momentary giddi- ness, flushed feel- ing. "Salty taste" in mouth.
3. C. R. 26	130 B. P. 120 80	135 94	130 90	126 85	124 84	122 82	1 min.	Onset 57 sec. Less 30 min. Fullness in head at end of 1 minute.
4. P. C. 23	130 B. P. 120 80	130 92	120 84	120 80			1 min.	Onset 70 sec. Less 20 min. Transitory giddiness and "metallic taste" in mouth.
5. R. C. 19	130 B. P. 116 74		124 84	122 80	118 76	116 74	3 min.	Onset 1 min. Less 24 min. "Metallic taste" in mouth.
6. R. C.* 19	130 B. P. 110 74	114 84	112 76	110 74	110 72		1 min.	Pallor due to previ- ous subcutaneous injection increased. Lips pale, head pallor persists several hours.
7. P. 25	130 B. P. 126 88	148 96	146 96	140 90	138 90	136 88	1 min.	Onset 70 sec. Less 22 min. Involves face and hands. None.
8. T. G. 24	130 B. P. 129 90	142 102	140 100	132 90	130 88	130 90	1 min.	Onset 67 sec. Less 20 min. Slight transient faintness. Per- sists sensations.
9. W. G. 31	130 B. P. 118 76	124 82	120 84	118 80	116 80	114 76	1 min.	Onset 75 sec. Less 20 min. Still pre- sent 44 min. Pal- lor involves face, neck and hands. Slight giddiness; desire to urinate.

No.	H.	1:30	B. P.	108.62	118.72	53	112.64	110.62	108.62	1 min.	Onset 69 secs. Less 20 mins.	Fullness in head, palpation, coldness in face.
		P.	P.	P.	P.	P.	P.	P.	P.			
10.	23					53	56	62	60			
						18	18	18	18			
11.	24					124.84	122.84	122.84	122.82	1 min.	Onset 70 secs. Less 40 mins.	None.
						92	90	88	86			
						18	18	18	18			
12.	24					122.88	116.76	116.74		1 min.	Onset 1 hour. Less 30 mins.	None.
						75	78	78				
13.	22					121.92	124.30	121.82	120.84	1 min.	Onset 75 secs. Less 12 mins. Total duration 28 mins.	Slight momentary fullness; mouth dry; palpation; desire to urinate. Periodic sensitization.
						81	80	80	72			
14.	28					65	65	75	72		Onset 53 secs. Less 20 mins. Duration 1 hour.	Slight transient fullness; end of 1 minute.
15.	21					110.74	104.70	102.70	102.70	3 mins.	Onset 85 secs. Less 8 mins. Duration 23 mins.	Preceding taste in back of mouth; end of 1 minute.
16.	26					130.80	124.75	126.74	125.74	1 min.	Onset 65 secs. Less 50 mins. Still present 85 mins.	Tingling in back of mouth; salivation; sensation of blushing; fullness in chest.
						76	74	64	68			
						17	17	19	18			
17.	27					128	120	116	114	1 min.	Onset 1 min. Less 21 mins. Duration 40 mins.	Cramplike pains lower abdomen, began at end of 5 minutes.
18.	27					130	126	122	120	3 mins.	Onset 1 1/2 mins. Duration about 50 mins.	Uterine cramps; bleeding from uterus and breast several hours later
19.	26					120.78	108.66	108.68	110.70	1 min.	Onset 1 min. Less 20 mins.	Slight transient fullness and "cold" taste in mouth.
						89	84	74	64			
						12	11	10	11			

* Injection given 40 mins. after previous subcutaneous injection (Table II, No. 7).

† Female.

TABLE II. *Schistosomus infections.*

Name and dose.	Dose in cc.	Blood pressure, etc., before and after injection.				Pallor.	Subjective symptoms.
		Before	1 min.	3 min.	5 min.	At end	
1. D. C. 26	1	B. P. 122/66 P. 73 R. 17	124/70 69 16	128/74 64 16	124/64 72 16	118/64 66 16	None. Onset 2 min. Slight at end of 80 minutes.
2. B. C. 19	1	B. P. 116/66 P. 73 R. 16	126/70 60 11	126/81 56 9	118/74 71 10	116/67 66 17	Pemphig-like sensa- tions at end of 50 minutes. Slight lockiness over temples.
3. A. D. 21	1	B. P. 122/54 P. 74 R. 18	128/72 64 21	128/72 62 20	116/64 66 19	116/64 68 19	Onset 3 min. Slight injection at end of 1 hour.
4. M. D. 25	1	B. P. 106/70 P. 54 R. 21	106/78 50 20	106/78 50 21	106/72 62 17	106/69 58 14	Onset 3 min. Tem- perature 100.4° F. Slight lockiness at 1 hour.
5. K. 30	1	B. P. 130/66 P. 84 R. 10	132/66 88 10	130/66 91 8	126/60 88 10	122/58 82 8	Onset 3 min. Slight injection at 1 hour. Slight rigidity at 13 minutes.
6. R. C. 19	1	B. P. 110/74 P. 68	112/76 62	112/76 62	112/76 72	112/74 72	Onset 20 min. Total rigidity at end of 2 hours. Involves face, neck, hands and torso.
7. R. C. 19	1	B. P. 107/76 P. 68	112/74 62	112/86 72	110/80 72	110/80 76 72	Onset 3 min. Total rigidity at 90 min. Involves face, neck, hands and torso.
8. R. C. 19	1	B. P. 106/75 P. 68	118/80 62	125/86 72	120/82 72	114/75 72	Onset 2 min. In- jection at end of 1 hour. Total rigidity at about 3 hours. Involves face, neck, hands and torso.
9. S. M. 28	1	B. P. 122/80 P. 68	120/84 62	132/94 72	136/90 72	130/86 72	Onset 3 min. Less injection at 30 min. Involves face, neck, hands and torso.
10. S. M.* 28	1	B. P. 130/86 P. 68	130/88 62	136/94 72	135/92 72	128/86 72	Pallor due to previous injection increased. Involves face, neck, upper and lower limbs.

* Injection over 35 min.; after previous schistosome infection (also table No. 6).

Subjective symptoms.

The most frequent subjective symptom is a momentary and slight sense of giddiness experienced $\frac{1}{2}$ –1 minute after an intravenous injection (see Table I). Often a peculiar sensation at the back of the mouth is described, generally during the first minute, as "tingling" or "dryness" or as a "metallic," "salty," or "peculiar" taste. Other less frequent symptoms are abdominal sensations attributable to peristaltic movements, desire to micturate and slight palpitation. In the only female subject used, and she had previously experienced menorrhagia, uterine cramps developed a few minutes after the injection and bleeding from the uterus and breast occurred several hours later. Generally the symptoms are of a very minor and undisturbing quality.

Few or no symptoms were noted after subcutaneous injections. Several subjects had slight griping sensations 15 minutes or more after the extract had been injected.

Paling of the skin.

Soon after an injection of infundin the skin of the face grows distinctly pale, this reaction having been noted after each of 42 injections in 21 subjects. The paling, most conspicuous in the cheeks, involves the entire face and neck, including the ears and mucous membrane of the lips. In the majority of cases the paling is intense, close attention being required to detect it only in a small number. With intravenous injections of 1/30–1/40 cc. unmistakable pallor of the hands and forearms was noted only a few times, slight or doubtful paling being more common; with subcutaneous injections of 1 cc., however, distinct paling of the hands and forearms was the rule, although the change was not as conspicuous as in the face. The skin of the trunk in which slight changes in colour are difficult to recognise, showed little or no change.

The onset of the pallor is preceded by a latent period which is longer after subcutaneous injections than intravenous ones. In the intravenous group the paling began about a minute (53–85 sec.) after the beginning of the injection, reached its height at the end of $2\frac{1}{2}$ minutes, and remained conspicuous for a further period of about 20 minutes. The total duration of the pallor varied from 23–85 minutes, being less than an hour as a rule. After subcutaneous injections the paling generally began at the end of 2–3 minutes and lasted for an hour or more, exceptionally persisting for 5 hours.

The occurrence of facial or generalised pallor after injections of pituitary extracts has been noted by a number of observers, but has generally been dismissed briefly^{1, 4, 5, 6, 7, 22, 25, 27, 34, 39}. In one clinical report the paling was considered to be one of "psychic origin." On rare occasions paling may be ascribed to such a cause (see footnote p. 360), but not usually. It occurs regularly in subjects in whom venous puncture alone is without effect and

reappears constantly when the dose is repeated either in a few minutes or after hours or days; it is maintained long after any uncomfortable sensations may have been experienced, persisting even if the individual happens to fall asleep. Finally, if the pallor is dispelled by effort or by the administration of amyl nitrite, it returns soon after the disturbing influence has been removed.

It is evident that the pallor is due to contraction of those vessels which are responsible for skin colour. In the cheek and forearm these vessels are mainly the minute collecting venules and those of the subpapillary plexus into which the latter empty, capillaries being scanty in these skin territories. A Zeiss-Greenough binocular microscope (62 diameters) was used to examine the skin of the face and mucous membrane of the lips in several subjects by means of Lombard's method, cedar wood oil being applied. The microscope was focussed on a small area in the cheek outlined in ink, and the vascular changes in this area observed before and after the extract was injected. Before the injection the sub-papillary venous plexuses and collecting venules and a few capillaries were clearly to be seen. After injection all the skin vessels began to diminish in calibre and at the end of 3-4 minutes the greater number of the venules and almost all the capillaries disappeared from view. The earliest detectable change occurs during the second half of the first minute. The visible vessels of the cheek which change least are the venules sufficiently large to be clearly seen with the naked eye. Similar changes are observed in the mucous membrane of the lips in which a relatively large number of capillaries can be seen. The capillaries and venules of the lip which were not seen to empty became distinctly narrower.

Several previous observations have demonstrated the power of pituitary extracts to constrict capillaries locally. Thus when a minute quantity of the extract is introduced into the skin a distinct area of blanching develops^{8, 16, 40}, which, as Carrier⁸ has seen microscopically, involves contraction of capillaries. I have also introduced minute quantities of undiluted infundin under the skin of the dorsal surface of the finger and hand, the flexor surface of the forearm, ear and cheek and found that the collecting venules and subpapillary venous plexuses disappear from view or become smaller along with the capillaries. In one case in which the local effect of infundin on dilated skin venules in the face was studied a distinct narrowing of these vessels was noted.

That the local blanching is due to an independent contraction of the capillaries and venules is demonstrated because it can be produced 5 minutes or longer after the circulation has been brought to a standstill by means of an occluding armlet, a method previously employed in this laboratory to demonstrate the active contraction of capillaries in response to adrenalin¹². Moreover Krogh²¹ has shown that perfusion of the hind leg of frogs with dilute solutions of pituitrin (1 : 50,000 to 1 : 1,000,000) results in partial contraction of the capillaries without visibly influencing the arteries.

From the preceding remarks it is clear that infundin exerts a powerful constrictive effect on the capillaries and venules. The sensitivity of these vessels to pituitary extract may be gauged from the fact that in suitable subjects it is possible to demonstrate paling after intravenous injections of as little as 1 200 cc. of infundin, an amount which if added to the calculated blood volume of an individual weighing 140 lbs. would represent a dilution of about 1 : 1,000,000 of infundin.

Blood pressure.

Numerous investigators have confirmed the early observations of Oliver and Schäfer³¹ who showed that pituitary extracts induce a rise of blood pressure in mammals²². The rise is frequently preceded by a conspicuous fall²² which is attributed by Abel and his co-workers^{2, 3} to the presence of preformed vasodilator substances (histamine and histamine-like compounds) in both freshly prepared and commercial extracts of the gland: though other authors¹⁴ deny the presence of histamine in pituitary extracts in detectable amounts.

The changes in the blood pressure resulting from injections of pituitary extracts in man have been studied by a number of observers, but the results are conflicting. Claude and Porak¹⁰, Leschke²⁵, and Houssay²², employing freshly prepared extracts, and Silva³⁹ employing "endoipofisina," noted a distinct fall of pressure in the majority of cases, the fall in systolic being greater than in the diastolic pressure. Behrenroth⁶ employing hypophysin (1 2 cc.) in normal subjects, Rosenow³⁶, pituglandol (1 cc.), and Beço⁵, pituitrin obtained inconstant results after intramuscular and intravenous injections. Schmidt³⁸, studying a group of febrile patients suffering from various diseases, found that intramuscular injections of 1-1½ cc. pituitrin produced no constant nor conspicuous change in the systolic pressure but caused in the majority of cases a rise of 10-15 mm. of Hg. in the diastolic pressure. Tode⁴¹, employing subcutaneous injections of pituitrin and pituglandol in patients with various diseases of the circulatory and autonomic nervous system, noted in most cases a rise in both the systolic and diastolic pressures.

Results. The changes in the blood pressure after intravenous injections of infundin are summarised in Table I. Thirteen observations were made on 11 subjects employing 1 30 cc., 3 observations on 2 subjects with 1 40 cc. and 1 observation on 1 subject with 1 20 cc.: the results were similar after 20-40 secs., both systolic and diastolic pressures rose rapidly and generally reached a maximum at the end of the first minute. After remaining at this level for 2-3 minutes the pressure gradually returned to its former level at the end of 5-10 minutes. The average rise in the systolic pressure was 9 mm. of Hg., and in the diastolic pressure 10 mm., the extremes for the systolic rise being 3 and 18 mm., and for the diastolic rise 4 and 16 mm..

Subcutaneous injections (5 observations in 5 subjects with $\frac{1}{2}$ cc. of infundin and 5 observations in 3 subjects with 1 cc.) resulted in an average rise of 9 mm. in the systolic pressure and 12 mm. in the diastolic pressure, the extremes in the systolic rise being 0 and 19 mm. of Hg. and in the diastolic rise 0 and 24 mm.. The rise began at the end of the first and more often after the second minute. The highest readings recorded were generally those obtained at the end of 3 minutes. In no instance in either group was an injection followed by a fall of pressure which could be attributed to the direct action of the drug.* Intravenous injections of 1-150-1-200 cc. infundin diluted with 1-2 cc. Locke's solution were without effect on the blood pressure.

Pulse.

Pituitary extracts generally slow the heart in animals²⁶. The retardation occurs also after the vagi are cut or paralysed by atropine²³, and in the perfused isolated heart¹⁷. In the intact animal the rise of pressure may also be involved in the slowing of the pulse. Sinus arrhythmia, heart-block, extrasystoles and other disturbances of rhythm have been noted in man^{11, 25}, and similar changes have been seen in animals^{11, 18, 22}.

Sixteen observations were made on 14 subjects who received infundin intravenously (Table I). A diminished pulse rate was noted 10 times, the fall averaging, however, only 6 beats per minute and reaching its maximum at the end of the third minute as a rule. The greatest fall observed was 14 beats per minute (Table I, Nos. 2 and 14). In 7 cases the slowing was preceded by an increase in the rate, and in 4 acceleration alone was noted. After 3-5 minutes the pulse rate rapidly returned to its former level.

When the extract was given subcutaneously (6 observations in 5 subjects) the decrease in rate, which occurred in all but one case, was more conspicuous, averaging 10 beats per minute (Table II). No disturbances of rhythm were discovered; but it is to be remarked that the amounts of pituitrin given were far less than those which have been seen to produce arrhythmias in animals.

Respiration.

Mummery and Symes³⁰ noted shallow respiration after injections of pituitary extracts in cats and dogs. Houghton and Merrill²¹, on the other hand, noted acceleration in dogs. Paukow³³ observed two distinct periods of apnoea in rabbits after large intravenous injections. Fröhlich and Pick¹⁵ concluded that Paukow's secondary apnoea is due to constriction of the

* On two occasions a profound fall of blood pressure was witnessed after an intravenous injection of 1/30 cc. infundin, but on both occasions the fall was associated with nausea, profuse perspiration and conspicuous slowing of the pulse. In one of these instances the subject fainted. The records of neither are included in the tables since the phenomena observed were clearly fainting attacks of the kind described by Cotton and Lewis¹³, and could not be attributed to the action of the extract.

medullary arteries, since it fails to appear when the vasoconstrictor action of the extract is annulled by the simultaneous administration of amyl-nitrite. Roberts³⁵ has repeated the experiments of previous observers and concludes that apnoea in rabbits and shallow respiration of cats are due to anaemia of the respiratory centre resulting from cerebral vaso-constriction. His conclusion is strengthened by finding that other vaso-constrictor substances, *e.g.*, adrenalin, ergotoxin, and barium chloride, exert a similar effect on respiration. In man Leschke²⁵ noted periods of apnoea after intravenous injections of 5-10 cc. of freshly prepared extract. Van den Velden¹², McKinlay¹, and Behrenroth⁶, on the other hand, found pituitary extracts to be without appreciable effect.

Results. In 8 subjects who received a single dose of infundin intravenously, shallow respirations for a brief period, were noted 3 times (Table I). In 3 the respiratory rate was diminished by 2, and in 1 by 3 per minute. In 5 subjects who received a single dose of infundin subcutaneously (Table II.), shallow respirations were noted once, associated with a fall of one in the respiratory rate. In 2 subjects, the rate fell from 10 to 7, and 16 to 9 per minute, respectively, but the respiratory excursion was increased instead of diminished.

Venous pressure.

The venous pressure was estimated by Moritz and Tabora's method²⁹. The readings were made from the meniscus of the citrate solution, oscillating with respiration, and were corrected to the level of the sternum. After obtaining a series of constant readings the injection was given and the readings continued at 30 seconds intervals for 12-36 minutes. The results of 5 intravenous injections (1-30 cc.) and 1 subcutaneous injection (1 cc.) in 6 subjects are recorded in Table III. Sometimes a small immediate rise was noted and in others an inconspicuous gradual fall, but on the whole the results indicate that infundin in the doses employed produced no constant nor material change in the venous pressure.

Rosenow³⁶ employing intramuscular and intravenous injections of pituglandol in large doses (1 cc.) observed a gradual fall of venous pressure in the majority of cases.

Outline of the heart.

Groedel's orthodiagraph was used to obtain records of the heart outline. The readings were made with the subject sitting and holding his breath at a controlled phase of inspiration. Several outlines were made before and after injecting infundin intravenously. The first record after the injection was obtained at the end of 1-2 minutes and subsequent records were taken at 2-3 minute intervals for a short period. In observations on 3 subjects no measurable change in the dimensions of the cardiac outline could be detected.

TABLE III.
Urems pressure in cc. of water (Moritz and Tidoni's method).

Name.	Infusulin.	Excess injection	1 min. after.	2 mins. after.	3 mins. after.	5 mins. after.	10 mins. after.	15 mins. after.	20 mins. after.	30 mins. after.	Arterial pressure.
C. B. ...	130 cc. intravenously	2.3	3.1	3.2	3.3	3.8	3.9	3.7			Table I, No. 2.
C. J. F. ...	" "	1.5	1.0	1.9	1.8	1.4	0.9	0.4	0.2		Table I, No. 7.
J. G. ...	" "	2.9	2.8	3.0	3.1	5.2	2.9				Table I, No. 8.
R. W. ...	" "	2.8	3.5	3.8	3.3	3.8	3.1	2.3	2.0	1.5	Table I, No. 15.
P.	" "	6.0	8.0	6.5	6.5	6.2	5.3	4.5	4.4	3.6	Table I, No. 13.
R. C. ...	1 cc. subcutaneously	2.2	2.5	2.7	2.9	3.0	3.7	4.0	3.5	4.2	Table II, No. 7.

Volume of the limb.

The left leg or right forearm was placed in a plethysmograph containing water at constant temperature, and allowed to soak for a period of 20-30 min. Infundin (1/20-1/40 cc.) was then injected intravenously, the beginning and end of the injection being signalled.

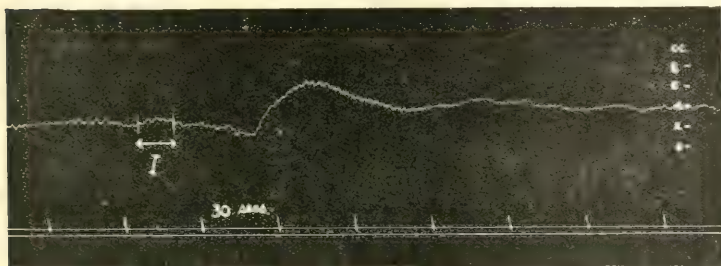


Fig. 1 ($\times \frac{1}{2}$). Subject, R. C. Volume curve of left leg showing expansion of limb after intravenous injection of infundin (1/30 cc.). I.=injection. B. P. before 116/74 and 3 minutes after injection 124/84 (Table I, No. 5). Onset of pallor=1 minute after beginning of injection.

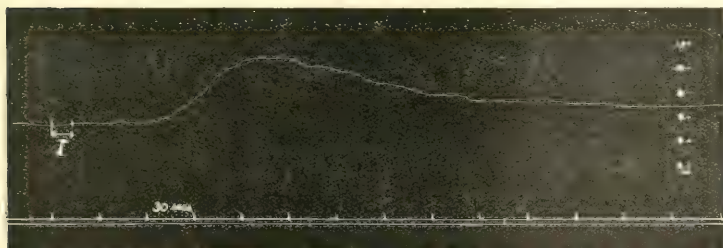


Fig. 2 ($\times \frac{1}{2}$). Subject I. W. Volume curve of left leg showing expansion of limb after infundin. I.=injection. B. P. before 125/74 and 1 minute after injection 134/82 (Table I, No. 16). Onset of pallor = 65 seconds after beginning of injection.

Six subjects were used. In each instance after a period of latency averaging about 1 minute (39-75 sec.) the volume of the limb began to increase reaching a maximum at the end of about 100 sec. (Figs. 1 and 2). After reaching the summit the curve fell more or less rapidly, remaining slightly above its previous level in all but one case, in which it fell somewhat below it. The actual increase in volume was 2.0-5.6 cc., the limb volumes

being 500 cc. to 1800 cc.; it was accompanied by blood pressure rises averaging 7 mm. of Hg. systolic and 8 mm. diastolic. Pituitary extracts produce constriction when tested on strips of the femoral artery³² or when perfused through the dog's hind leg²⁶; moreover, pituitary extracts cause intense vaso-constriction of the limbs in the intact animal (dog), but the reduction in volume is preceded by a brief period of expansion²⁸. In all probability the transient expansion of the limb represents a passive change resulting from constriction of the splanchnic arterioles during the height of the blood pressure reaction. Rosenow³⁷, who also noted ephemeral distension of the limb (arm), after intravenous injections of pituitary extract (pituitandol and hypophysin in doses of 0.5-2.0 cc.) in man, arrived at a similar conclusion, but failed to show that the blood pressure was regularly elevated during the period of expansion.

The conspicuous contraction of the limb, noted by Magnus and Schäfer²⁸, was not observed in these experiments. In the single instance in which the volume curve indicated in my observations a contraction of the limb, the reduction in volume was inconspicuous.

Rate of blood flow.

Hewlett and Zwaluwenburg's²⁰ method was used to estimate the blood flow to the limbs. The plethysmograph described in the previous section was used. The veins were occluded by suddenly throwing a pressure of 38-45 mm. of Hg. into a broad pneumatic cuff applied to the corresponding thigh or arm, and the rate of increase in the volume of the limb measured. The temperature of the limb was maintained constant.

The results of 13 determinations in 8 subjects employing intravenous and subcutaneous injections are summarised in Table IV. The results were inconstant, a slight fall or a slight rise or a stationary rate being recorded. Taken as a whole, the figures indicate that the rate of blood flow to the limbs is not conspicuously altered by injections of infundin in the doses here employed.*

Rate of œdema formation.

When the veins of a limb are suddenly occluded by a 40 mm. pressure, the volume of the limb rapidly increases till the veins fill; if the compression is maintained the swelling continues (at a slower rate), and this further rise is due, in the main, to œdema, and its steepness measures the rate of œdema formation.

* Hewlett¹⁹ noted a tendency for the blood flow in the arm to increase after intramuscular injections of pituitrin; but the temperature was not maintained at a constant level in his observations. Christie and Stewart⁹ report an increase in the blood flow to the hands in a patient with diabetes insipidus complicated by dermatitis of the hands.

TABLE IV.

Name.	Intend.	Temp. C.	Volume of limb, cc.	Blood flow in cc. per 100 cc. of limb volume before and after injection.		B.P. and remarks.
				Before.	5-10 mins. 15-20 mins. 20-30 mins.	
1. P. C.	1-20 cc. intravenously	34	1440	1.72	1.96 1.86	Table I. No. 1.
2. R. C.*	" "	32.5	1775	1.92 2.06	2.17 2.27	Table I. No. 5.
3. R. M.*	" "	33	1385	1.06	0.76 1.17	Table I. No. 11.
4. H.*	" "	32	1640	1.14 1.11	0.91 1.48	Table I. No. 10.
5. S.*	" "	32	500†	1.22	1.19	
6. I. W.*	" "	31	1610	0.89	0.94	Table I. No. 16.
7. S. M.*	1-40 cc. "	36	1800	1.66 1.82	2.48 2.14 2.71	
8. S. M.	$\frac{1}{2}$ cc. subcutaneously	36	1800	2.71	2.14 2.51	Injection given 37 minutes after intravenous injection (1-40 cc.) (this table, No. 7).
9. R. C.	1 cc. "	33	1900	2.10 2.36	2.41 2.10	Table II. No. 6.
10. R. C.	" "	32	1900	1.54	1.42 1.51	Table II. No. 8. Readings in connection with edema curve (Table V. No. 2).
11. E.	" "	36	1450	4.75	4.36 4.75	
12. S. M.	" "	33	1610	1.46	1.32 1.22	Table II. No. 9. Readings in connection with edema curve (Table V. No. 1).
13. S. M.	" "	33	1610	1.22	1.48 1.42 1.18 1.30	Table II. No. 10. Injection 35 minutes after subcutaneous injection (1 cc.) (this table, No. 12).

* Readings in connection with edema curve.

† Right leg only.

TABLE V.
Rate of œdema formation.

Name.	Pressure mm. of Hg.	Volume of limb cc.	Temp. C.	Volume increase per min. in cc. per 100 cc. of limb.		
				0-10 mins.	10-20 mins.	20-30 mins.
1. S. M.†	Control.					
	Infundin 1 cc. subcutaneously at end of 15 mins.	40 compression cuff	33.5°	0.084§	0.090	0.092
2. R. C.‡	Control.					
	Infundin 1 cc. subcutaneously at end of 10 mins.	40 compression cuff	33°	0.076	0.074	0.045 0.027*
3. E.	Control.					
	Infundin 1/40 cc. intravenously before	hydrostatic pressure	32°	0.064	0.064	0.055
4. S.	Control.					
	Infundin 1 cc. subcutaneously before	hydrostatic pressure	32°	0.084	0.047	0.032
			40°	0.066	0.051	0.053
			39.5°	0.087	0.038	0.027
			36.8°	0.069	0.055	0.062
			36°	0.128	0.044	0.024

* 30-35 minutes after compression was begun.

† For b. p. and blood flow see Table II, No. 9, and Table IV, No. 12, respectively.

‡ For b. p. and blood flow see Table II, No. 8, and Table IV, No. 10, respectively.

§ Representing an actual increase of volume of 13.9 cc.

Extensive studies of œdema so produced have been carried out in this laboratory by Dr. Drury, to whom I am indebted for help in these observations. The details of the method will be described by him at a later date. The rate of swelling of the limb is recorded over a period of 30-35 minutes, the pressure in the cuff and the temperature of the water being maintained at a constant level; observation is then repeated after a suitable interval and under 1 cc. infundin administered subcutaneously and the two compared. Observations were made on 2 subjects, the injection being given 10 and 15 minutes, respectively, after the occlusion was begun. In two additional cases a compression cuff was not applied, the rates of œdema formation in the dependent leg under the influence of hydrostatic pressure being recorded. In one of these infundin was given intravenously (1.40 cc.), and in the other subcutaneously (1 cc.).

The results are summarised in Table V, and will be discussed together. During the first 5-10 minutes after injection the rate of swelling was either inconspicuously diminished or actually increased a little (see volume of limb). The rate of swelling then progressively diminished, reaching its minimum at the end of 15-20 minutes or more after the injection, the greatest reduction noted varying from 41.8 per cent. (*R. C.*) to 64.0 per cent. (*S. M.*). The most pronounced change occurs at a time when the main effect on the blood pressure has subsided and the pallor is at its height. These results indicate that infundin conspicuously decreases the rate of œdema formation. The blood flow to the limb, estimated immediately after the greatest observed reduction in the rate of œdema production and compared with earlier readings, was either slightly diminished or increased.

DISCUSSION AND CONCLUSIONS.

Evidence has been brought forward to show that pituitary extract (infundin) when injected into human beings not only contracts the arterioles but also the capillaries and minute venules. Paling of the skin is constant and will occur after minute intravenous doses. Though most conspicuous in the face and neck, the pallor is by no means confined to these areas, frequently also affecting the limbs, especially when the extract is injected in larger doses subcutaneously. Paling is due to an observed contraction of the vessels responsible for skin colour, namely, the capillaries, the collecting venules and those of the subcapillary plexus. The effect on these vessels is the same as that produced locally by introducing pituitary extracts into the skin, the local blanching being clearly due to constriction of the capillaries (Carrier), and, as I have shown, this constriction is active and affects the venules as well. Additional reasons to those already stated for believing that the vessels involved are not emptied passively as a result of arteriolar constriction are that the paling can be produced by doses of the extract too small to raise blood pressure, and in other cases the persistence of pallor long after the blood pressure has resumed its formal level; it is

also to be noted that pallor has been recorded when as a result of pituitary injection, the blood pressure has fallen.

The effect of hypophyseal extracts on the arterioles can be gauged most readily by noting the effect on the blood pressure. In a series of observations here recorded, a small but distinct elevation of the arterial pressure was the rule, the diastolic pressure being changed rather more than the systolic. The rise of pressure was inappreciable in a few cases: in no instance was a fall encountered. It is brief. The absence of more conspicuous and permanent blood pressure change is somewhat remarkable in the presence of what is often profound pallor. It is to be remembered, however, that the profound pallor is facial, and the extent to which tissues, other than the skin, are affected is not known.

The transient expansion of the limb at the height of the blood pressure reaction furnishes indirect evidence that the splanchnic arterioles are constricted during this period, reduction in volume, consequent on increased tone of the minute skin vessels, being masked by the altered distribution of the blood during the period of splanchnic constriction. Plethysmographic evidence of vascular constriction in the limbs, after the preliminary passive expansion, although demonstrable in animals, was not clearly obtained in these experiments, a secondary diminution of limb volume having been the exception rather than the rule, even when the limb was distinctly pale.

Estimations of the rate of blood flow after injections of infundin gave inconstant results, a small rise or fall or no appreciable change being noted. This result is not wholly surprising if two opposing actions in the limb are simultaneously in play, the one, a passive effect of constriction in the splanchnic area, tending to augment the blood flow, and the other, a locally increased vascular tone, tending to diminish it.

The results of the experiments on œdema formation are consistent with the observed contraction of the capillaries and venules of the limbs. Since the reduction in the rate of œdema formation in the limb is recorded at a time when the blood pressure has returned to normal and the pallor is still at its height, there is little doubt that the effect observed, and this is conspicuous, is due to change in the capillaries and venules. The change is not due to concomitant alteration of blood flow to the limbs, and must be ascribed either to diminution in the size of these vessels or to altered permeability of their walls.

The slowing of the heart which occurs in more than half the cases, though definite, is not conspicuous. The bradycardia, if present, is frequently preceded by a brief period of acceleration. No disturbances in rhythm were noted in these observations.

Note.—While this paper was in the press, a report by Kolls and Geiling (*Journ. Pharmacol. and exper. Therap.*, 1924, xxiv, 67) appeared on the action of pituitary liquid (Armour) on unanæsthetised and anaesthetised dogs. Employing large doses intravenously (1/4-1 cc.), these observers noted intense paling of the skin and mucous membranes, and by viewing the vessels of the ear by Lombard's method found the capillaries to be contracted. They also noted dilatation and diminished output of the heart.

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SUPERNORMAL RECOVERY PHASE, ILLUSTRATED BY TWO CLINICAL CASES OF HEART-BLOCK.*

By THOMAS LEWIS and A. M. MASTER.

(*Cardiac Department, University College Hospital Medical School, London.*)

THE two cases of heart block here recorded present an unusual feature which, so far as we are aware, is hitherto undescribed. They appear to illustrate a brief overswing in the recovery curve of the muscle implicated, comparable to the supernormal phase which has been described by Adrian and Keith Lucas^{1,2} in the recovery curves of nerve and muscle after response. The first case, which we now proceed to describe, was originally under the care of Professor T. R. Elliott, at whose request the case was examined and to whom we are correspondingly indebted.

First observation.

H. N., a married man of 56 years, was admitted to hospital on July the 16th, 1924, in a state of collapse. A few days later he gave the following history.

From birth his left side has been paralysed, this condition proving to be an old standing hemiplegia with athetosis: at 24 years he acquired typhoid fever; at 53 he suffered from influenza and has had bronchitis since this illness. Apart from his cough there were no symptoms until the day of his admission, and his health was good.

On July the 16th, while taking tea, he became faint and lost consciousness for a few minutes. On recovery he felt alarmed, was giddy, nauseated, sweating and experienced intermittent flushing and was brought to hospital.

A very thin man, he was found to be in a state of collapse, the pulse rate being irregular, and its rate 40 to 48 beats per minute. He continued in this state until the morning of the 17th, when he again lost consciousness for a few minutes. During the morning of this day the pulse rate was slower, falling from time to time to 20 to 25 beats per minute, but remaining irregular. At such times the man became very pale. There were recurring phases

* Observations undertaken for the Medical Research Council.

during which the pulse quickened to about 70 beats per minute and this more rapid action was accompanied by very distinct flushing of the skin. In the afternoon the pulse was somewhat more rapid but remained irregular; the series of curves here described was taken during this period. The chest was emphysematous; the cardiac impulse was imperceptible, the heart sounds faint but seemingly normal in character. The arteries were thickened, the systolic blood pressure was 90 mm. Hg. A capsule of amyl nitrite inhaled failed to affect the pulse rate. He was given a hypodermic dose of 1.50 grain of atropine. The pulse rate rose from 26 to 34 during the following hour and continued to rise to 70 during the next 12 hours. On the morning of the 18th he was placed on a mixture containing 5 minims of tincture of belladonna. On the 19th the general condition had further improved, the pulse rate remaining at 70 to 80 beats per minute and regular; the heart's mechanism on this day was perfectly normal, and it remained so during the rest of his stay in hospital, the belladonna tincture being omitted on the 22nd. The atropine and belladonna appear to have had little or no effect on his heart's action, recovery occurring gradually and spontaneously; the blood pressure rose to 116 mm. Hg. His strength increased rapidly, and on the 12th and 16th of August his teeth were extracted. He stood these operations well and was sent to a convalescent home on the 20th of August. His complement fixation test proved negative; the urine was normal.

Cardiac mechanism.—A selection from the curves taken on the 17th is shown in Fig. 3. In Fig. 3a the meaning of the slow pulse action is evident; we have to deal with complete heart block. Over the first half of this curve both the auricles and the ventricles are beating regularly and their rates are 23 and 89, respectively. The complete heart-block is undisturbed throughout the curve, with the exception of a premature beat of the ventricle marked *x* in its centre. Now the ventricular complexes of the curve, with this solitary exception, are of one form; they are of aberrant type and resemble those of beats arising in the left ventricle. The exception, namely, the premature beat, is normal in type. Its initial deflections are of short duration and resemble those of the normal heart beats of this subject, obtained two days later and when the patient was convalescent (Fig. 4). During the first half of the curve, a not unusual relation between auricular and ventricular systoles is manifested, each fourth auricular systole falls simultaneously with a ventricular systole; but, owing to the lack of a simple mathematical relation between the rate of the auricular and ventricular beating, these auricular beats gradually move position in relation to the ventricular systole with which they fall: thus P^2 falls in the isoelectric period between the deflections *S* and *T*, P^6 falls at the upstroke of *T*, P^{10} halfway up the upstroke, and P^{11} almost at the summit of *T*, and P^{18} just a little later. Falling at this instant it is responded to by the ventricle. That this is so is clearly shown by Fig. 3b and by a number of similar records taken at the

same sitting. In Fig. 3*b* the ventricle responds to the auricle on five occasions, to P^3 , P^7 , P^{11} , P^{21} and P^{25} ; these P summits all fall upon that phase of ventricular systole which intervenes between the summit of T and a point near the end of T ; when P falls at any phase of systole or diastole other than that described, no premature contraction of the ventricle is seen. Fig. 3*b* shows another curious disturbance, to which we shall refer only briefly; the form of P changes, becoming of lower amplitude and triphasic.

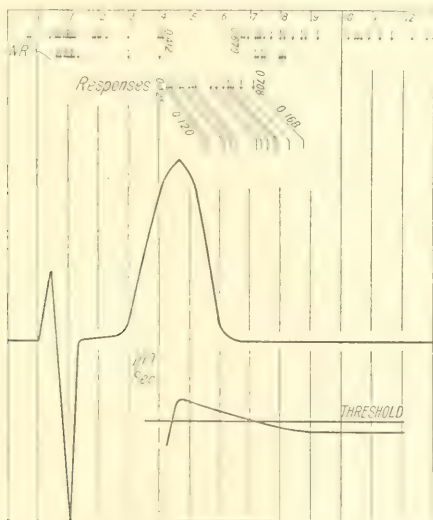


Fig. 1. (Case 1.) A chart showing the auricular systoles to which the ventricle responds and to which it fails to respond (*N.R.*) in time relation to ventricular systole. Abscissæ in tenths of a second; the zero line of time corresponds to the beginning of the ventricular complex.

The change becomes established at P^{13} and continues to the end of the curve. This change was seen in many curves and was associated with slower beating of the auricle: presumably it was due to a change in the site of the pacemaker. Thus, it occurs again in Fig. 3c, at P^{12} , and the more usual form reappears towards the end, at P^{22} . These changes in the form of P were unconnected with the question of response or no response of the ventricle, as the published records sufficiently demonstrate. We are content to note them and shall consider them no further, as they do not affect the observation of chief importance. To complete the evidence, we have taken the whole

batch of records and have plotted all those *P* deflections of normal and upright form* which fall during the period of systole or near to it and, similarly, we have plotted a selection of those auricular waves which fall in diastole (Fig. 1): to plot all such auricular waves and to show them to the end of ventricular diastole is unnecessary: it is sufficient to state that though they fell at all phases of diastole, not one produced response of the ventricle beyond the 0.7 time line. The diagram shows clearly that there is a brief phase of the ventricular cycle which is peculiar: it commences sharply 0.42 of a second after the beginning of the first ventricular deflection *R* and ends somewhat less sharply about 0.70 of a second after the same zero point. An auricular systole falling in this period sends an effective impulse to the ventricle; falling at any other phase of systole or of diastole, the ventricle fails to respond.[†] When response occurs it occurs after an average interval of 0.143 of a second: this conduction time is well within normal limits. When the responses are studied, it is notable that those which correspond to the earliest auricular systoles are followed by the shortest transmission intervals, those which occur latest are followed by the longest transmission intervals. The series of intervals is shown in the diagram, the first being 0.120 of a second, and the last being 0.168 of a second in duration. As the end of the responsive phase is reached the passage of effective impulses to the ventricle becomes more hesitating: this is contrary to usual expectation: it is the rule, as is widely recognised, that the *P R* interval becomes longer, and not shorter as in this instance, when the period of preceding rest is short. The reason for reversal of the usual relation is obviously that the phase over which response occurs is passing into one in which response cannot occur: the hesitation to respond increases to the point of refusal.

A further illustration remains to be described, namely Fig. 3c. In this record, one of several, the events are similar to those in the first two curves, that is to say, there is the picture of complete block, broken at two points (*P*²⁹ and *P*¹⁵). The first disturbance is of a kind so far unnoticed: there are three successive responses to auricular systoles (*P*²⁹, *P*¹⁰ and *P*¹¹). The three corresponding ventricular complexes are normal in every respect: they should be compared with those of Fig. 4. This period is properly regarded as one in which the normal heart rhythm has become temporarily restored. The reason why, when the auricular systole falls at a suitable instant, the ventricle responds once in most instances and twice or thrice successively on occasion, becomes evident when the relation of the auricular

* Had we included the abnormal *P* deflections the result would not have been different, but the measurements in the last case would have been less accurate.

[†] The arrows on the diagram and the values given above refer to the beginning of *P*. Where this upstroke of *P* has been obscure we have used its summit for measurement and have made a suitable allowance to find its beginning. When neither the upstroke nor summit could be clearly defined, and this has very occasionally been the case, the point midway between the adjacent *P* waves has been taken.

systoles to preceding ventricular systoles is examined. In all other instances in these records, when the ventricle responds to the auricle, the succeeding auricular systole falls clear of the premature ventricular systole. In the present instance, the auricular rate being a little quicker than usual, the auricular systole P^{10} falls actually on the end of the preceding ventricular systole; it falls therefore in the susceptible phase of that systole. Similarly with P^{11} , for this also falls on the end of the preceding ventricular systole; but since it falls relatively a little later than P^{10} , the response occurs with more hesitation. The P - R intervals of the three successive cycles, when accurately measured show the following values: 0.133, 0.150 and 0.164 of a second. The next auricular systole (P^{12}) is delayed and falls clear, and consequently response fails. This curve, while bringing additional support to the interpretation placed on the remainder, forms a curious illustration: for, as is seen, the reappearance of block is associated with *slowing* of the auricular rhythm; a relation of a very unusual kind and one to which we shall again refer.

Before proceeding to comment upon these records, a second series of curves, taken from a different patient, will be described.

Second observation.

The second series of records (Fig. 5) was taken from a patient eleven years ago: the clinical history is no longer available; but it is known that the curves were from a middle-aged man, suffering from a chronic condition of partial heart block. The records will be described for simplicity in respect of their chronological order. The first (Fig. 5a) is a simple example of partial block, displayed by a P - R interval of nearly 0.4 of a second in duration. The remaining records are part of a large series taken during a single sitting six weeks earlier. Fig. 5b presents a somewhat higher grade of block than does Fig. 5a. The P - R intervals are prolonged and occasional responses fail. P^6 and P^7 lie isolated in long diastoles. This is the condition usually described as that of "dropped beats." When a beat is dropped out in this way, the ventricle here contracts in response to its own rhythm. Two examples of such escape (R^5 and R^6) are shown in the curve and, with each of these ventricular systoles, a rhythmic auricular systole coincides (P^4 and P^8 , respectively). It is to be noticed that each of these buried auricular summits immediately succeeds the downstroke of the R deflection, in fact the upstroke of P coincides with the deflection S . A similar mechanism is displayed in the third curve (Fig. 5c). In this instance there are three escaped beats and P^4 , P^7 and P^{10} coincide with them; but the precise relation of the auricular to the corresponding ventricular systole varies a little. P^7 falls earliest, P^{10} falls a little later and P^4 falls latest in systole. P^4 is followed by a premature beat of the ventricle. The last curve (Fig. 5d) also displays three escaped beats with coincident auricular systoles; and each

of these last is in this instance followed by a ventricular beat. All three of the buried auricular systole fall relatively late in the coincident ventricular systoles. These and the remaining unpublished examples make it abundantly clear that the anomalous and premature beats of the ventricle are in reality responses to the preceding auricular beats. The ventricular beats of the series, marked *x*, are presumably anomalous because they are premature, and some aberration has occurred during the transmission of the corresponding impulses to the ventricle. A chart, prepared in the same fashion as Fig. 1, is shown in Fig. 2. The arrows at the top of the chart, which represent auricular contractions, are arranged in two lines, those to which there is no response above, and those to which there is response below. The auricular

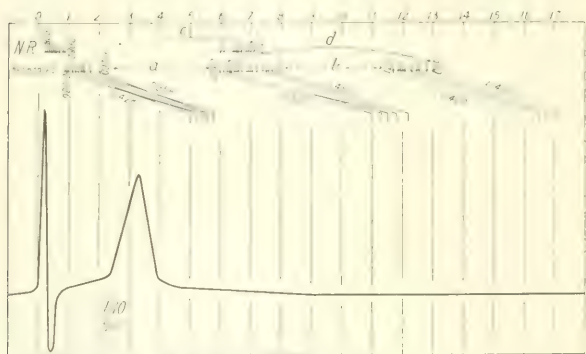


Fig. 2. (Case 2.) A chart constructed similarly to that of Fig. 1.

systoles as a whole are arranged in three groups: those which fall with the ventricular systole (the buried group); those which fall in early diastole and those which fall in later diastole. This grouping is consecutive to the arrhythmia with which we are dealing; as its result portions of the cycle remain untested. The auricular systoles to which there is no response fall in two groups and those to which there is response in three groups. Of the last, two are separated by the untested gap *b*. There is no reason to doubt that response would happen to any auricular systole falling in this gap *b*, and that the period of response is at least as extensive as the bracket *d*. As we follow the auricular systoles backwards over this period *d* it is found that the *P-R* intervals rise in value to 0.50 of a second; overlapping the beginning of this period, is a period (between the 0.6 and 0.7 time lines) in which a group of auricular systoles yield no response. We then come to the untested gap *a*. It is hardly to be doubted that auricular systoles

falling in the last part of gap *a* would rarely yield response and that the period of no response may be indicated by a bracket such as *c*, though the precise length of this phase is not ascertainable. Starting now at the extreme left of the chart, we encounter first a short period during which the auricular systoles fail to yield response; these fall with the initial deflections of the electrocardiograms, and are shortly followed by a group of auricular systoles which yield responses. The beginning of the group of responses is sharply defined at 0.08 of a second from the zero line and extends as far as the 0.20 second line. We then enter once more the untested gap *a*. It is probable that auricular systoles falling in the first part of this gap would yield responses. The *P-R* intervals, when response actually occurs, average 0.411 of a second; although the first response measures 0.428 and the last 0.358, the intervals as a whole are irregular and show no very decided tendency to decrease as they are traced to the right. The average *P-R* interval in the groups of responses at the beginning and ending of period *d* is 0.479 and 0.436, respectively.

To sum up the ventricular cycle as a whole; in its initial phase auricular systoles yield no responses; responses begin when the auricular systoles fall 0.08 of a second after the upstroke of *R* and this phase extends to the 0.2 line and probably ends near the 0.4 line; the *P-R* intervals of this phase are the shortest. A period follows in which presumably there would be no response (part of bracket *c*), but this is only demonstrable at its termination and here it overlaps a period of response, which is continued throughout the rest of the cycle. Thus the case in its most important feature resembles the first case described; both are cases of heart-block; in both responses of the ventricle occur in a very early phase of diastole, while in later phases of diastole responses either fail entirely or occur after more hesitation.

COMMENTS.

The observations upon the first case described are the most complete and the conclusions which can be drawn from them are therefore to be emphasised. The events in this case, so it seems to us, are interpretable on one assumption only, namely, that a process (or processes) of recovery in the tissues, following response, passes through a phase comparable to what has been described as the supernormal phase. When nerve, somatic or cardiac muscle is tested by means of stimuli of known strength, it is found that during the stage of actual response, these tissues are refractory to stimulation, and that during their recovery from this state of absolute refractoriness they pass through a condition of relative refractoriness; that is to say, they will respond at first to stronger stimuli but not to weaker ones. The minimal strength of stimulus required gradually decreases until it becomes constant. The curve of recovery, ascertained in this way, rises somewhat abruptly and passes through a rounded shoulder into the threshold line. In certain circumstances, as Adrian and Keith Lucas¹ & ² have shown, the curve rises at first above the

threshold at an early phase, and falls to the threshold a little later. It is this early rise above threshold which has been termed the supernormal phase, and it has been shown to be manifested by tissues bathed by fluids in a relatively acid state. Strictly speaking, perhaps, we are not entitled to speak of a phase of supernormality in the present case, since the tissues will not respond to stimuli in the later phases of diastole. If we assume that the natural stimuli at this time would be adequate if they fell on normal tissue, then the recovery curve lies during this phase below the normal threshold line, as it is represented in Fig. 1. To explain the mechanism of response over the whole cycle, we must suppose either that the natural stimuli vary in strength in conformity with the recovery curve of this figure, or that the variation in response is due to change in the responsiveness of the tissues. Either would in fact be adequate as an explanation, but since the curve follows a type known to represent tissue recovery, the last explanation is at present the more acceptable. We suppose therefore, that this clinical patient exhibits the phenomenon displayed by nerve and muscle bathed by fluids which are relatively acid: we suppose further that the line of recovery as a whole is depressed.* During the later phases of diastole the state of recovery is such that the natural impulses are inadequate: only during a short and early period of diastole, where there is an overswing of the recovery curve, and where it consequently crosses the threshold line, are they adequate. In this sense we may speak of the phase of response as a phase of supernormal recovery: the *P-R* intervals in this phase are actually on the lower limits of normality: if we regard them as shorter than normal for this patient, then we should be dealing with a phase of supernormality, using the term in the absolute as well as in the relative sense. The normal intervals estimated two days later averaged 0.156 of a second (Fig. 4).

We have avoided so far two questions which arise. Firstly, as to the precise tissue involved and, secondly, as to the precise tissue function which is at fault.

In regard to the tissue involved, this may be either the auriculo-ventricular node, the bundle, its branches, or the ventricle itself. Now a good deal of evidence has been accumulated to show that in heart-block arising from diverse causes, such as increased rate of auricular beating¹¹, asphyxia¹², vagal stimulation⁷ and poisoning with such bodies as strophanthin¹¹, etc., the tissue concerned lies in the main stem of the junctional tissues, and it is the auriculo-ventricular node or its junction with the auricle that appears usually to be affected. *A priori*, therefore, the junctional tissue is most suspect in the present instance. Amongst other evidence put forward for the junctional tissues as the susceptible point is the fact that in general, when heart block occurs, there is no evidence from the form of the

[* * The same general depression is presumably present in a muscle lying in a relatively acid medium, and the use of the term supernormal in that instance is open to a similar objection.

electrocardiographic curves that the block occurs below the level of the bundle's division: on the contrary, the evidence obtained from these curves points to the block being situated above this level. Similar evidence exists in the present case. When the impulses are effective, the form of the ventricular complex is normal (responses marked x in the records), showing that the ventricle is supplied by impulses passing normally through both the right and left stem of the bundle and normally distributed through the end branches; and this is so whether the response is prompt or is hesitating. If the block were situated in the arborisation or in the ventricle itself, this could hardly occur unless, when the response was hesitating, a uniform degree of hesitancy was displayed by several or a large number of tissue elements scattered throughout the ventricle. From analogy with other instances of heart block and from this internal evidence, we conclude that the blocking point was probably situated in the junctional tissues. Incidentally it is to be stated that in previous records in which block of the type seen in this patient has occurred, block unassociated with abnormally long transmission intervals, *Wenckebach* have been found in the tissues named⁹ (see also Mobitz's recent paper)¹⁰. When the overswing of the recovery curve is drawn in relation to the abscissa of our chart (Fig. 1), it might be drawn to correspond with the ventricular responses, or at an intermediate point, according to the view taken of the precise blocking point. It has actually been placed on early abscissæ.*

As to the precise tissue function at fault the facts are less clear. The conduction intervals, when response occurs, are all within normal limits, the slight widening which occurs as the responses are traced from right to left may be regarded as a return to normal from supernormality. There is no evidence in these intervals to suggest that a hypothetical function "conductivity" is implicated. The block displayed is of a type long recognised, namely, one in which ventricular beats are abruptly dropped, the mechanism being otherwise quite normal: in this it contrasts with the more usual form, where lack of response is foreshadowed by notable prolongations of the conduction intervals, as in our second case. The passage from block to normal transmission and back again is abrupt in cases of the first type; it is abrupt where it occurs in the curves of our patient, and this is consistent with the speedy recovery of a completely natural heart mechanism (Fig. 4). Fig. 3, in reality displays a short period of normal rhythm, buried in the centre of a phase of complete block. The case is comparable in this respect to those rather rare cases in which, without warning, the ventricle ceases to beat for periods sufficient to produce unconsciousness, while before and after the standstill of the ventricle, the conduction intervals are perfectly normal (see a recent paper⁹ and references there given). There are also

* To correspond to block in the node, the curve should come at a somewhat later phase than it is here represented; but, as the precise time relations are indeterminable, it is placed for simplicity opposite the auricular systoles.

instances of chronic complete heart-block, such as that investigated by Wilkinson¹⁵ in which, at the end of a period of ventricular standstill, the ventricle responds to each auricular beat. It is noteworthy that, in that instance, the response occurs as an association of a quickened auricular rhythm, as it does in Fig. 3*c* also. In thinking of the function at fault in our first case, it will be evident that we have variations of "excitability" chiefly in mind, though our interpretation is taken as far as seems justifiable if we conclude that the changes occur in the responsiveness of the tissue concerned.

The second case differs in one essential from the first, in that long transmission intervals are always displayed whether the responses are in early or in late diastole. There is at no time a phase during which the conduction intervals even approach normality. Nevertheless the events in early diastole are obviously to be interpreted as overswing of the recovery curve towards normal. As to the tissue involved in this second case, the direct evidence is less clear than in the first, since the early responses yield an anomalous form of ventricular response. Interpreting these anomalous beats as they are now usually interpreted, a local defect in a bundle branch is to be assumed, which is developed as a consequence of the beat's prematurity. This defect is distinct from that which yields long transmission intervals from auricle to ventricle, since the usual form of ventricular response is normal. The assumption of a branch defect, however, leads us to the conclusion that, while the recovery curve of the tissues responsible for the main and permanent defect is swinging towards normal, recovery in the bundle branch is depressed. This does not invalidate the assumption. The anomalous beat represents a defective ventricular response of some kind and, however we explain it, the same difficulty is experienced, since the defect is coincident with the phase of greatest recovery in the tissues, which conduct the impulse from auricle to ventricle, treated as a whole.

In explaining our second case it is unnecessary to postulate an overswing in the recovery curve of a separate function "conductivity." The separate-ness of "excitability" and "conductivity" so called is not proved, and the long transmission intervals, displayed by the second case, are not necessarily due to changed rate of fibre conduction, but may be explained equally well in terms of impulse strength or, preferably, in terms of responsiveness of the tissue involved. It would be impossible adequately, and at the same time briefly, to discuss the general and fundamental problem of muscle function raised; and, as its full consideration here would be out of place, it must suffice if the more relevant points are dealt with summarily. A defect in conduction rate, while it may explain lengthened *P-R* intervals, does not explain an absence of response; an absence of response means that the impulse fails to proceed beyond a certain point. There is, so far as we are aware, no sufficient evidence that such failure to proceed can be attributed to a defect in a primary and independent function "conductivity"; the

instant the impulse fails to proceed, the idea at once comes that the succeeding section of tissue refuses to accept the stimulus, either because that stimulus is inadequate, or the tissue is at the moment inexcitable to stimuli of natural strength. Moreover, a defect in "conductivity" need not be invoked, even in explaining prolonged conduction intervals. Changes in the rate of conduction may be conceived in terms of stimulus strength and responsiveness. Thus conduction rate may be reduced by partial refractoriness of the muscle fibres, a state in which some fibres fail to respond owing to the greater duration of their individual refractory periods¹⁰. If we accept the membrane theory of propagation, then the rate of conduction depends upon the strength of the action current, a stronger current being capable of stimulating at a greater distance, and upon the responsiveness of the tissue (see Lillie¹³ and others^{3, 8, 4}). Actually, a prolonged *P-R* interval is no proof of lowered conduction rate either in individual muscle fibres, or from fibre to fibre in the heart. The general tendency of physiological thought to-day is towards a simplified conception of cardiac muscle function, a conception in which "conductivity" and "excitability" find no place as separate and distinct qualities.* It may seem improbable that the phenomenon of overswing in the recovery curve exhibited has in each of our two patients precisely the same underlying cause, seeing that they display different types of heart-block. When it becomes known in what fundamental respect, if any, these two types of heart-block differ from each other, then only shall we be in a position to decide whether the overswing has in the two a common basis of origin. The terms in which the overswing is described must so far as possible be the terms of physiological thought; these still remain unstable.

The cases here reported, and especially *Case 1*, are of interest from a further point of view. In a recent series of articles, Kaufmann and Rothberger^{14, 6} have explained certain forms of irregularity, hitherto termed extrasystolic, as resulting from the interference of two separate rhythms (parasystole). There is a variety of case which they desire to include in this category, in which the coupling of extrasystoles to the beats which precede them is accurate or almost so, and in which it is also necessary to assume that the rhythm responsible for the premature beats is the faster of the two. In our present *Case 1*, a slow and regular ventricular rhythm is disturbed by occasional responses to a rhythm of much faster rate arising in the auricle: the resulting ventricular rhythm is often a bigeminal action of the ventricle, the bigeminy displaying almost accurate coupling (Fig. 3*b*). The events therefore are parallel, though they are not identical, with those which Kaufmann and Rothberger postulate in their cases. One of the chief difficulties encountered in accepting certain of Kaufmann and Rothberger's cases as instances of parasystole, is that of understanding how two rhythms, of independent rate and having no simple mathematical relation to each

* Some remarks and references to the views of other writers, relevant to this question, will be found in a recent paper by one of us⁸.

other, can yield in one and the same heart chamber responses which tend to arrange themselves in accurate couples. It is easier to understand that they can yield an irregularity in which the coupling is inaccurate. The present case illustrates one mechanism by means of which coupling more or less accurate can result. The chamber, in which the irregularity occurs, beats in response to a slow rhythm, and is also capable of responding, during the phases of supernormal recovery from these responses, to impulses which are received from a second and more rapidly acting centre. Response to this second centre is confined, however, to a short phase of the recovery curve, the stimuli being inadequate in all other parts of the cycle, and more or less accurate coupling consequently results. Inadequacy of the stimuli over the last parts of diastole is also a necessary postulate in the theory of parasystole as it is put forward, when it is supposed, as it usually is supposed, that the rhythm underlying the extrasystolic beats is a fast one. This phenomenon, which has been named "*austrittsblockierung*" in the theory, has remained hypothetical and Licherto does not seem to have found so clear an illustration as the present one to support it.

SUMMARY.

1. A clinical case is described in which complete heart-block is disturbed by the transmission of impulses from auricle to ventricle. These responses are seemingly in every way normal but occur over a limited reach of the cycle. The tissue involved is thought to be the auriculo-ventricular node. The phase of peculiar responsiveness falls early in the cycle and is comparable to the overswing of the recovery curve which has been termed the "supernormal phase."

2. A second case is described, which presents a similar phenomena, though it differs from the first in manifesting long conduction intervals between auricle and ventricle.

3. The cases described lend some support to the theory of parasystolic irregularities put forward by Kaufmann and Rothberger: their bearing upon this theory is briefly discussed.

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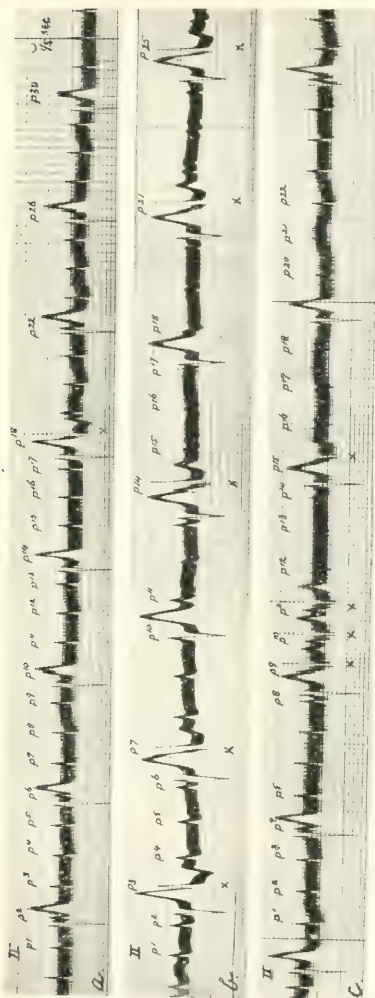


FIG. 3 (79). Case 1. Three electrocardiograms taken at one sitting, by lead I, L, and showing complete heart-block interrupted by occasional isolated or grouped responses of ventricle to auricle. In this and subsequent figures, vertical lines are at fifth-second intervals, and the ordinates represents 1 millivolt to 1 centimetre.



FIG. 4 (79). Case 1. A similar curve, taken two days later.

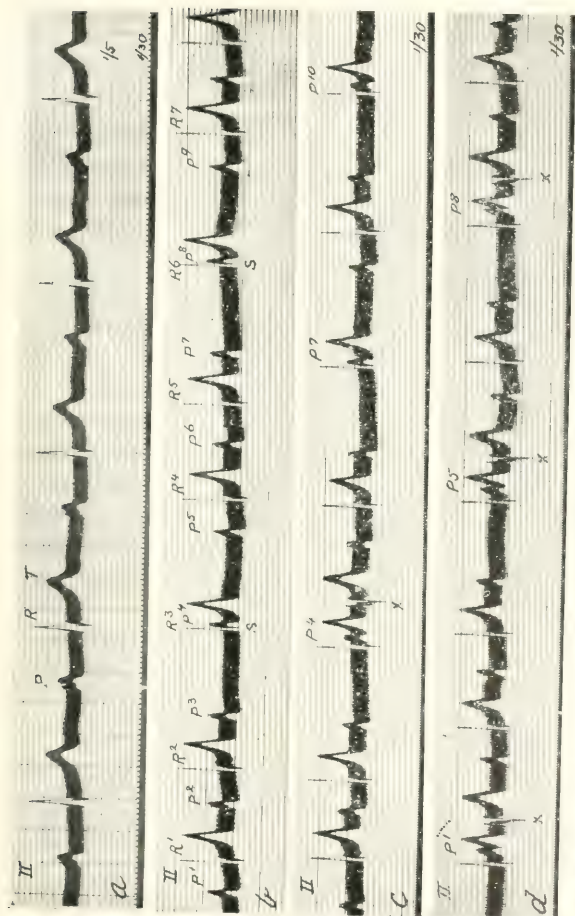


Fig. 5, *a, b, c, d*. Case 2. Four electrocardiograms by lead II showing heart-block with widened conduction intervals, *a*, taken on the 28th of July, 1913; *b, c, d*, taken on the 12th of June, 1913. In records *c* and *d* early responses to the ventricle are seen, marked *x* on the records. The time is recorded below in thirds of a second.

THE INFLUENCE OF HYDROGEN-ION CONCENTRATION UPON
CONDUCTION IN THE AURICLE OF THE PERFUSED
MAMMALIAN HEART.*

By A. N. DRURY and E. COWLES ANDRUS.†

(From the Cardiac Department, University College Hospital Medical
School.)

In a previous paper by one of us¹, it has been shown that the duration of the *P-R* interval is intimately associated with the hydrogen-ion concentration of the fluid used to perfuse the heart, being shortened by perfusates more alkaline, and lengthened by perfusates less alkaline than normal. As this interval represents the time taken by the excitation wave to traverse not only the auricle but also the specialised tissue of the *A-V* node and bundle it does not indicate the influence of the hydrogen-ion concentration upon the rate of conduction in auricular muscle. To investigate this point in more detail the present study was undertaken.

The dog's heart was used exclusively in these experiments: it was isolated and perfused by the method already described¹, except that it was not removed from the thorax. Locke's solution of standard composition was used as a perfusate, which was thoroughly oxygenated, warmed to 37° C. in glass coils placed in a thermostatic tank and perfused through the heart under a constant pressure of oxygen at 50-80 mm. of mercury. The reaction of the perfusate was adjusted by means of decinormal hydrochloric acid or sodium hydroxide, and checked with phenol red against a standard indicator series.‡ The abnormal perfusates were usually allowed to flow for five or ten minutes when a normal perfusate was again introduced.

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† Fellow in Medicine of the National Research Council, U.S.A.

‡ Perfusate of three different hydrogen-ion concentrations were used, namely, P_H 7.0, P_H 7.4, and P_H 7.8.

The heart was slung in the pericardium to the thoracic walls and the right auricle stretched out by means of a thread attached to the tip of the auricular appendix, in the dorsal wall of which a small cut was made through which the perfusate flowed from the auricle, ensuring a rapid change of fluid throughout this chamber. The perfusate which discharged both from the pulmonary artery and auricle escaped from the thorax through openings made in the chest wall below the level of the heart. The conduction rate was examined by placing in line upon the auricular muscle two or three pairs of non-polarisable electrodes: each pair was connected to a galvanometric string, and timed the arrival of the excitation wave at the various points of contact on the auricular surface. Electrical records were easily obtained from the auricular muscle throughout these experiments which were of short duration: if, however, the heart was perfused for an hour or more, it became difficult to obtain satisfactory electrical records, possibly on account of the formation of œdema. The rate of conduction in the auricle was measured both with the heart beating naturally and responding to rhythmic shocks applied to the auricular muscle at rates ranging from 100-200 per minute. To test the effect of vagal stimulation upon conduction, acetyl-choline was used, since a short time after the perfusion commences stimulating the vagus in the neck fails to produce any effect. Doses of this drug, sufficient to produce a profound vagal effect, were introduced into the tubing carrying the perfusate and observations made as soon as ventricular standstill occurred. Owing to the sensitivity of the heart to lack of oxygen and to the difficulty of ensuring a sufficient supply of this gas, the experiments were carried through rapidly, and only exceptionally were readings taken more than one hour after the normal blood supply had been stopped.

Normal perfusates (P_{II} 7.4).

When the heart is perfused with a well-oxygenated Locke's solution of P_{II} 7.4 the rate of conduction in the auricle approximates 700-1,000 mm. per second, both in the naturally beating heart and in that responding to rhythmic shocks;* rates which are similar to those consistently obtained when the coronary circulation is intact. The rate of conduction remains the same whether the excitation wave is travelling from the body of the auricle to the tip or *vice versa*, the muscle conducting equally well in both directions. The electrical records obtained directly from the auricular muscle are normal in all respects. Such oxygenated perfusates are found to maintain constant and normal rates of conduction for long periods, but in the absence of oxygen lower rates prevail. This is shown by two experiments in which the oxygen in the perfusate was replaced by nitrogen, so that the

* "Controls" of tables following.

heart received an unoxygenated perfusate of $P_{H\ 7.4}$. Thus in Table I the rate of conduction in the auricle is decreased, but the effect does not become considerable for 5 to 10 minutes; the *P-R* interval is lengthened in the first minute. Auricular muscle, therefore, is much less sensitive to oxygen want than are the junctional tissues.

TABLE I.

Influence of oxygen-free perfusate upon transmission in the auricle. Perfusate ($P_{H\ 7.4}$).

<i>Dog.</i>	Muscle investigated.	Time in mins.	Rhythmic rate.	Auricular transmission interval.	<i>P-R</i> interval.
<i>U. V.</i>	Body of right auricle, 16 mm. of muscle.	0	163	0.0254	0.15
		1	163	0.0255	0.17
		4	163	0.0254	0.21
		7	163	0.0295	0.28
		10	163	0.0324	2:1 block
<i>U. Y.</i>	Appendix and body of right auricle. 24 mm. of muscle.	0	133	0.0325	0.12
		1	133	0.0339	0.13
		5	133	0.0327	0.22
		10	133	0.0357	2:1 block

Acetyl-choline, in doses sufficient to produce a profound vagal effect, has no constant or definite influence upon the rate of conduction in a perfused auricle beating rhythmically at rates of about 150 per minute (Table II). This result is to be expected, for observations upon the intact animal have consistently shown that vagal stimulation does not influence normal conduction in mammalian auricular muscle³.

More alkaline perfusates ($P_{H\ 7.8}$).

When a more alkaline perfusate is used ($P_{H\ 7.8}$) the rate of conduction is constantly increased, being usually about 10 per cent. faster than the normal value, but on occasions reaching 1,300 mm. per second. Such rates are given both by the heart beating naturally and by that responding to rhythmic shocks at rates of about 150 per minute (Tables III and IV). In the former circumstance, the sinus rate is also enhanced, so that the increased rate of conduction occurs with an accelerated heart rate, the two phenomena moving hand in hand. In the latter, the increased conduction occurs whether the excitation wave is travelling from the body of the auricle to the appendix or *vice versa* and uniform throughout the muscle. If, after 5 to 10 minutes, a perfusate of $P_{H\ 7.4}$ is again introduced both the conduction rate and the sinus rate fall, approximating their original values. The electrical deflections during the more alkaline perfusions show no obvious change in

TABLE II.
Influence of acetyl-choline upon transmission in auricle. Oxygenated perfusate (Pu 74).

<i>Dog.</i>	Muscle investigated.	Rhythmic rate.	Transmission interval.		Transmission rate.		Effect upon ventricular response.
			Control.	Ac. choline.	Control.	Ac. choline.	
<i>U.S.</i>	Tazza. 15 mm. of muscle	158	0.0210 0.0196	0.0190 0.0189	714 765	789 794	2 : 1 2 : 1
<i>U.T.</i>	Body of rt. auricle. 15 mm. of muscle	150	0.0149	0.0159	1007	940	<i>P. R.</i> lengthened.
<i>U.U.</i>	Body of rt. auricle. 15 mm. of muscle	163	0.0160	0.0149	940	1000	<i>P. R.</i> lengthened.
<i>U.V.</i>	Body of rt. auricle. 16 mm. of muscle	163 163	0.0215 0.0250	0.0219 0.0239	745 640	731 770	Vent. standstill. Vent. standstill.
<i>U.Y.</i>	Body of rt. auricle. 24 mm. of muscle	133 133	0.0325 0.0333	0.0356 0.0381	737 726	674 630	Vent. standstill.
<i>U.Z.</i>	Body and appendix of rt. auricle. 24 mm. of muscle	162	0.0310	0.0338	775	710	Vent. standstill.
<i>V.A.</i>	Body and appendix of rt. auricle. 24 mm. of muscle	130	0.0205	0.0211	1170	1140	Vent. standstill.

form from those obtained during a normal perfusion, but by fine measurement the upstroke of the deflection is found to be steeper. In one experiment the oxygen in the perfusion solution of P_H 7.8 was replaced by nitrogen. In this circumstance the conduction rate, after an initial increase, was slowed, but the latter effect was long delayed, appearing only after 25 minutes had elapsed (Table V), although the $P-R$ interval became prolonged in the first few minutes. With alkaline as opposed to normal perfusates, therefore, auricular muscle is able to withstand lack of oxygen for a considerably longer time without the conduction rate falling; the junctional tissues, however, are still very sensitive to oxygen lack.

TABLE III.

*Influence of hydrogen-ion concentration upon transmission in the auricle (naturally beating heart).
Normal to more alkaline perfusate.*

<i>Dog.</i>	Muscle investigated.	P_H .	Natural rate.	Transmission interval.	Transmission rate.
<i>U.R.</i>	Appendix of right auricle. 15 mm. of muscle.	7.4	107	0.0164	914
		7.8	115	0.0152	984
		7.8	145	0.0140	1070
		7.8	162	0.0155	980
		7.4	115	0.0146	1028
		7.4	115	0.0164	914
		7.4	115	0.0158	950
<i>U.S.</i>	Tania 15 mm. of muscle	7.4	85	0.0158*	950
		7.8	86	0.0149*	1007
		7.8	95	0.0155*	980
		7.8	92	0.0140*	1070
		7.8	95	0.0133*	1130
		7.8	97	0.0128*	1170
		7.4	80	0.0164*	915
<i>U.V.</i>	Body of right auricle. 16 mm. of muscle.	7.4	93	0.0176*	910
		7.8	139	0.0160*	1000
		7.8	162	0.0155*	1032
		7.8	162	0.0163*	981
		7.4	133	0.0207*	774
<i>U.W.</i>	Body of right auricle. 12 mm. of muscle.	7.4	150	0.0114	1050
		7.8	182	0.0092	1303
		7.4	158	0.0122	984
<i>U.X.</i>	Body of right auricle. 12 mm. of muscle.	7.4	120	0.0139	864
		7.8	150	0.0123	980
		7.8	133	0.0135	888
		7.4	111	0.0147	816
		7.8	136	0.0127	945
		7.4	115	0.0133	902
		7.4	122	0.0141	850

* Three pairs of non-polarisable electrodes were used in these experiments. The interval between the arrival of the excitation wave at the proximal and distal contact only is given, as the excitation was found to be travelling at the same rate through the two successive stretches of muscles.

TABLE IV.

*Influence of hydrogen-ion concentration upon transmission in the auricle (rhythmically driven heart).
Normal to more alkaline perfusate.*

<i>Dog.</i>	Muscle investigated.	P_{H_2}	Rhythmic rate.	Transmission interval.	Transmission rate.
<i>U.R.</i>	Appendix of right auricle. 15 mm. of muscle. Stim. at body.	7.4	125	0.0175	857
		7.8	125	0.0131	1145
		7.4	125	0.0152	987
		7.4	125	0.0162	926
<i>U.S.</i>	Tania. 15 mm. of muscle.	7.4	158	0.0191*	785
		7.8	158	0.0174*	862
		7.8	158	0.0172*	872
		7.8	158	0.0164*	915
		7.8	158	0.0161*	932
		7.8	158	0.0171*	877
		7.4	158	0.0206*	728
<i>U.T.</i>	Body of right auricle. 15 mm. of muscle. Stim. at body.	7.4	150	0.0156	962
		7.8	150	0.0145	1034
		7.8	150	0.0140	1071
		7.4	150	0.0174	862
<i>U.U.</i>	Body of right auricle. 16 mm. of muscle. Stim. at body.	7.4	163	0.0164	976
		7.8	163	0.0151	1060
		7.4	163	0.0158	1013
		7.4	163	0.0160	1000
<i>U.V.</i>	Body of right auricle. 16 mm. of muscle. Stim. at body.	7.4	163	0.0187*	856
		7.8	163	0.0160*	1000
		7.8	163	0.0163*	982
		7.4	163	0.0187*	856
		7.8	163	0.0170*	941
		7.8	163	0.0163*	982
		7.4	163	0.0215*	744
<i>V.H.</i>	Body of right auricle. 12 mm. of muscle. Stim. at tip of appendix.	7.4	177	0.0126	952
		7.8	177	0.0105	1143
		7.8	177	0.0107	1122

* See footnote, Table III.

TABLE V.

Influence of oxygen-free perfusate upon transmission in the auricle. Perfusate (P_{H_2} 7.8). Controlled auricular rate = 171 per minute.

<i>Dog.</i>	Muscle investigated.	Time in mins.	Auricular transmission interval.	<i>P-R</i> interval.
<i>V.N.</i>	Body of appendix. 16 mm. of muscle.	0	0.0280	0.15
		3	0.0272	0.16
		6	0.0254	0.17
		7	0.0242	0.25
		13	0.0233	0.25
		16	0.0246	0.26
		20	0.0271	0.30
		28	0.0318	2 : 1 block.
		33	0.0351	2 : 1 block.
		45	0.0424	2 : 1 block.

Profound vagal stimulation, brought about by injecting acetyl-choline, has no definite or constant influence upon the enhanced rates of conduction (Table VI).

TABLE VI.
Effect of acetyl-choline upon transmission in the auricle. Organized perfusate (Pn 7-8).

Dog.	Muscle investigated.	Rhythmic rate.	Transmission time.		Transmission rate.		Effect of acetyl-choline upon vent. response.
			Control.	Ac. choline.	Control.	Ac. choline.	
C. T.	Body of right auricle, 15 mm. of muscle	150	0-0145	0-0149	1034	1007	<i>P. R.</i> lengthened, <i>P. R.</i> lengthened.
			0-0140	0-0156	1070	962	
U. U.	Body of right auricle, 16 mm. of muscle	163 163	0-0151	0-0145	1060	1103	<i>P. R.</i> lengthened, <i>P. R.</i> lengthened.
			0-0221	0-0187	724	856	
U. Y.	Body of right auricle, 16 mm. of muscle	163	0-0163	0-0174	982	920	Vent. standstill. Vent. standstill.
			0-0163	0-0172	982	930	
U. W.	Body of right auricle, 12 mm. of muscle	182	0-0114	0-0126	1053	1000	2:1 Vent. standstill.
				0-0129		930	
U. Y.	Body and appendix of right auricle, 24 mm. of muscle.	133 133	0-0326	0-0387	736	620	Vent. standstill. Vent. standstill.
			0-0347	0-0366	692	656	

Less alkaline perfusates (P_H 7.0).

If the heart is perfused with less alkaline fluids (P_H 7.0) the rate of conduction is always decreased. Tables VII and VIII show the results of a series of perfusions of 5-10 minutes' duration interposed between normal perfusions. With the heart beating naturally (Table VII) the less alkaline perfusates always retard the cardiac rate, so that a slow rate of conduction and beating are associated. In hearts responding to rhythmic stimuli a decreased conduction rate is observed whether the wave is forced from the body or tip of the auricular appendix. The fall in conduction rate is apparently uniform throughout the muscle. Upon returning to a normal perfusate (P_H 7.4) the rate of conduction rises to its original value and generally the original sinus rate is restored. If the oxygen in such a perfusate

TABLE VII.

*Influence of hydrogen-ion concentration upon transmission in the auricle (naturally beating heart).
Normal to less alkaline perfusate.*

<i>Dog.</i>	<i>Muscle investigated.</i>	<i>P_H.</i>	<i>Natural rate.</i>	<i>Transmission interval.</i>	<i>Transmission rate.</i>
<i>U.R.</i>	Appendix of right auricle. 15 mm. of muscle.	7.4	116	0.0135	1111
		7.0	91	0.0163	920
		7.4	125	0.0128	1172
<i>U.S.</i>	Tania 15 mm. of muscle	7.4	80	0.0164*	915
		7.0	65	0.0171*	877
		7.4	79	0.0160*	938
<i>U.V.</i>	Body of right auricle. 16 mm. of muscle.	7.4	133	0.0207*	773
		7.0	60	0.0230*	696
		7.4	125	0.0223*	717
<i>U.W.</i>	Body of right auricle. 12 mm. of muscle.	7.4	158	0.0122	984
		7.0	90	0.0170	706

* See footnote, Table III.

is replaced by nitrogen the rate of conduction falls profoundly, and reaches in a few minutes such values as 400-300 mm. per second. Moreover, in these circumstances the rate of conduction fails to be uniform throughout the muscle, the excitation wave slowing down in speed as it passes through the muscle from the point stimulated (Table IX). For instance, if three paired non-polarisable electrodes are placed equidistantly and in line upon the body and tip of the appendix, and rhythmic shocks are applied to the body of the auricle, in some instances the rate of conduction between the proximal and middle electrodes is quicker than between the middle and distal electrodes; in other instances the distal electrodes fail to show a response of the underlying muscle to alternate stimuli, while the middle and proximal electrodes still record a response to all. Later, the muscle under the distal

TABLE VIII.

*Influence of hydroxy-ion concentration upon transmission in the auricle (rhythmically driven heart).
Normal to less alkaline perfusate.*

<i>Deg.</i>	Muscle investigated.	Pn.	Rhythmic rate.	Transmission interval.	Transmission rate.
U.N.	Appendix of right auricle. 12 mm. of muscle. Stim. at base.	7.4	100	0.0177	678
		7.4	100	0.0188	638
		7.0	100	0.0237	506
		7.0	100	0.0222	540
		7.4	100	0.0216	556
		7.4	100	0.0194	619
	Stim. at tip of appendix	7.4	100	0.0174	690
		7.4	100	0.0186	645
		7.0	100	0.0234	513
		7.0	100	0.0212	566
U.R.	Appendix of right auricle. 15 mm. of muscle. Stim. at body.	7.4	136	0.0158	949
		7.0	136	0.0183	820
		7.4	136	0.0158	949
U.S.	Tania. 15 mm. of muscle.	7.4	145	0.0198*	758
		7.4	145	0.0198*	758
		7.0	145	0.0226*	664
		7.0	145	0.0232*	647
		7.4	145	0.0206*	728
		7.4	145	0.0197*	762
U.V.	Body of right auricle. 16 mm. of muscle. Stim. at body.	7.4	163	0.0215*	744
		7.0	163	0.0262*	611
		7.0	163	0.0286*	559
		7.4	163	0.0234*	684
U.Z.	Appendix and body of right auricle. 24 mm. of muscle. Stim. at body.	7.4	162	0.0310*	774
		7.0	162	0.0385*	623
		7.0	162	0.0451*	532
V.A.	Appendix and body of right auricle. 24 mm. of muscle. Stim. at body.	7.4	130	0.0205*	1171
		7.0	130	0.0354*	678
		7.4	130	0.0249*	965
V.B.	Appendix and body of right auricle. 24 mm. of muscle. Stim. at tip of appendix.	7.4	130	0.0381*	630
		7.0	130	0.0408*	588
		7.0	130	0.0428*	560
		7.0	130	0.0497*	483

* See footnote, Table III.

electrode entirely fails to respond, while that beneath the middle and proximal electrodes still responds rhythmically. Slowing of the wave in its passage, and failure to reach the more distal parts of the auricle, occurs whether the rhythmic stimuli are applied to the body or appendix of the auricle. Moreover, in one experiment the rhythmic shocks were applied at the beginning to the body and later to the tip of the appendix: the wave slowed in its course in both circumstances; it travelled slower as it moved towards the tip of the appendix in the one case, towards the body of the auricle in the other. The fact that stimulation of the body of the auricle or the tip of the

TABLE IX.
Influence of oxygen free perfusate upon transmission in the auricle. Perfusate (P_H 7.0).

Dog.	Position of electrodes.	Rhythmic rate.	Response at electrodes.			Transmission time.		Transmission rate.	
			I	II	III	I-II	II-III	I-II	II-III
U.W.	Body and appendix of right auricle. 24 mm. between electrodes. Stim. at body of auricle	171	1:1	1:1	1:1	0.087	—	276	—
		171	1:1	2:1	—	0.119	—	202	—
		171	1:1	2:1	—	0.160	—	150	—
		171	1:1	0	—	0.162	—	148	—
V.A.	Body and appendix of right auricle. Stim. at body. Two successive stretches of 12 mm. of muscle. Stim. at body of auricle	130	1:1	1:1	1:1	0.0245	0.0352	490	341
		130	1:1	1:1	1:1	0.0300	0.0400	400	300
		130	1:1	1:1*	1:1	0.0407	0.0485	295	242
		130	1:1	1:1*	0	0.1000	—	120	—
V.D.	Body and appendix of right auricle. 24 mm. between electrodes. Stim. at tip of appendix	200	1:1	1:1	1:1	0.0406	—	591	—
		200	1:1	2:1	—	0.0435	—	552	—
		200	1:1	2:1	—	0.0506	—	474	—
		200	1:1	2:1	—	0.0656	—	366	—
		200	1:1	1:1	—	0.0659	—	364	—
		200	1:1	2:1	—	0.0750	—	320	—
		200	1:1	1:1	—	0.0770	—	312	—
		200	1:1	0	—	—	—	—	—
V.F.	Body and appendix of right auricle. Two successive stretches of 12 mm. of muscle. Stim. at tip of appendix	200	1:1	1:1	1:1	0.0342	0.0473	351	254
		200	1:1	1:1	1:1	0.0430	0.0460	279	261
		200	1:1	1:1	2:1	0.0444	0.0484	270	248
		200	1:1	1:1	2:1	0.0453	0.0409	265	293
		200	1:1	1:1	2:1	0.0446	0.0248	269	484
		200	1:1	2:1	2:1	0.0518	0.0486	232	—
		200	1:1	2:1	2:1	—	—	—	—
		200	1:1	2:1	2:1	—	—	—	—
U.Z.	Body and appendix of right auricle. Two successive stretches of 12 mm. of muscle. Stim. at body of auricle	162	1:1	1:1	1:1	0.0295	0.0360	407	333
		162	1:1	1:1	1:1	0.0314	0.0391	382	307
		162	1:1	1:1	1:1	0.0335	0.0382	358	314
		162	1:1	0	0	0.0348	0.0454	345	264
	Stim. at tip of appendix								

* Alternation.

appendix is followed by block as a distance indicates that this phenomenon is not due to unequal distribution of the perfusate, but depends upon the distance which the excitation wave has already travelled through the impaired muscle. Similarly the slowing of the wave during its progress, the preliminary to actual block, is shown to be due to a peculiar and uniform condition of the muscle. Unequal influence of the perfusate could produce the phenomenon in one region only, and not in a region which changes according to the site of stimulation. In some experiments the excitation wave failed to travel

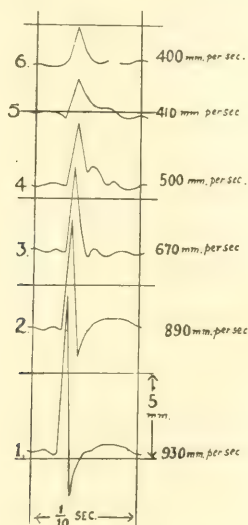


Fig. 1. A series of electrical records obtained from the same pair of non-polarisable electrodes during a perfusion with an oxygen free Locke solution of $\text{pH } 7.0$ to illustrate the alteration in the form of the complex as the rate of conduction is slowed. The conduction rate is written by the side of each complex. The ordinates of the curves as reproduced represent a time interval of 1-10th of a sec., the abscissæ a distance of 5 mm.

in a straight line: when this happens it is recognisable, and in such experiments the transmission intervals are affected and slowing of the wave in its progress cannot be determined.

The electrical deflections taken during the less alkaline perfusion show definite and very obvious changes. Their amplitude is decreased and the steepness of the upstroke and downstroke of the deflections is relatively and absolutely diminished, as perfusion continues. In Fig. 1 is shown a

series of intrinsic deflections obtained from the same pair of non-polarisable electrodes during a perfusion with P_H 7.0 in which the oxygen had been replaced by nitrogen. The original records were projected with a lantern and magnified 8 times, outlined on paper and have subsequently been reduced. The rate of conduction between two fixed points of the auricle, obtained by direct measurement, is written by the side of each deflection. These curves, which were obtained in their order of notation over a perfusion period of about seven minutes, show very definitely the changes described as the rate of conduction in the auricle decreases. The electrical deflections are little altered when the conduction rate is slightly decreased, but when the rate of conduction is considerably decreased, the deflections are heavily degraded. Consequently when the excitation wave slows down in its progress from point to point, the electrical deflections obtained from the several points show a corresponding diminution. The proximal record largely retains its original form: the middle is definitely and the distal record considerably degraded.

This phenomenon, namely, slowing down of the excitation wave in its passage, has been described as occurring when oxygen free perfusates of P_H 7.0 are used: but it is to be stated, that, under the conditions of experiment, it occurs also during prolonged perfusions with oxygenated fluids of P_L 7.0. We are of the opinion that lack of oxygen plays its part in both circumstances: for a heart after long perfusion with oxygenated fluid probably lacks oxygen, and on occasion intra-auricular block produced by unoxxygenated perfusates of P_H 7.0 can be relieved by oxygenated perfusates of the same ionic concentration. Our observations show that well-oxygenated perfusates of P_L 7.0 first decrease conduction rate uniformly throughout the muscle: later if the perfusion is continued long enough this uniformity is lost, and the feature of slowing during progression is added. Unoxxygenated perfusates of P_H 7.0 act similarly but more rapidly and certainly. When the excitation wave slows down to a halting point in its course through the affected muscle, we have to deal with a phenomenon comparable to that termed "decrement"^{2A}, and supposed to occur when an impulse fails to pass through a region of nerve which is narcotised.

Acetyl-choline in doses sufficient to produce a profound vagal effect was frequently injected both when the rate of conduction was slightly decreased and when the excitation wave slowed in its course. In the former circumstance its action was indefinite (Table X), though on the whole the rate of conduction tended to increase. In the latter (Table XI) acetyl-choline constantly not only caused the wave to travel faster, but also to penetrate further into the muscle, actual block being relieved: the effect on the slowing of the wave on its course was as a rule not complete, that is to say, uniform conduction rates from point to point were not as a rule re-established. The electrical deflections were correspondingly changed by such injections, the amplitude being increased, and the upstroke and downstroke of the deflection becoming steeper. In the presence of slowing of the wave in its

TABLE X.

Influence of neopelcholine upon transmission in the auricle. Organophosphorus (P. 749).

Dog.	Muscle investigated.	Rhythmic rate.	Transmission interval.		Transmission rate.		Effect upon vent. response.
			Control.	Ac. choline.	Control.	Ac. choline.	
C. S.	Tennis, 15 mm. of muscle	158	0.0268	0.0224	560	670	Vent. standstill.
		158	0.0195	0.0265	769	732	Vent. standstill.
		158	0.0198		758		
C. W.	Body of right auricle, 16 mm. of muscle	163	0.0286	0.0273	559	586	Vent. standstill.
U. Z.	Body and appendix of right auricle, 24 mm. of muscle.	162	0.0385	0.0408	623	588	Vent. standstill.
		162	0.0451	0.0466	532	515	Vent. standstill.
V. A.	Body and appendix of right auricle, 24 mm. of muscle.	130	0.0334	0.0288	678	833	2:1
		130	0.0366	0.0367	656	654	Vent. standstill.
V. B.	Body and appendix of right auricle, 24 mm. of muscle.	129	0.0408	0.0354	588	678	Vent. standstill.
		129	0.0428	0.0363	561	661	Vent. standstill.
		129	0.0497	0.0474	483	510	Vent. standstill.

TABLE XI.

Influence of acetylcholine upon transmission in the auricle. Oxygen free perfusate (P_u 7.0).

Dog.	Muscle investigated.	Rate.	Response at electrodes.				Transmission time.				Transmission rate.	
			Control.		Acetylcholine.		Control.	Acetylcholine.	Control.	Acetylcholine.	Control.	Acetylcholine.
			I	II	III	I	II	III				
U.W.	Appendix of right auricle 20 mm. of muscle. Stim. at body of auricle.	171	1:1	2:1		1:1	1:1		0.119	0.129	168	155
		171	1:1	0		1:1	2:1		—	—	—	—
V.A.	Body and appendix of right auricle. Two suc- cessive stretches of 12 mm. of muscle. Stim. at body of auricle.	130	1:1	1:1	1:1	1:1	1:1	1:1	0.0245	0.0352	490	341
		130	1:1	1:1*	1:1	1:1	1:1	1:1	0.0107	0.0495	295	242
		130	1:1	1:1*	0	1:1	1:1	2:1	0.110	0.0680	109	—
U.Z.	Body and appendix of right auricle. Two suc- cessive stretches of 12 mm. of muscle. Stim. at body of auricle	162	1:1	1:1	1:1	1:1	1:1	1:1	0.0295	0.0360	407	333
		162	1:1	1:1	1:1	1:1	1:1	1:1	0.0314	0.0391	382	307
	Stim. at tip of appendix	162	1:1	1:1	1:1	1:1	1:1	1:1	0.0335	0.0382	358	314
		162	1:1	1:1	1:1	1:1	1:1	1:1	0.0348	0.0454	345	264
		162	1:1	0	0	1:1	1:1	1:1	—	—	—	—

* Alternation.

† Alternation abolished.

course, with its accompanying and progressive degradation of the complexes, the records from the several points were all improved in the sense that the deflections increased in amplitude and the disparity between the amplitudes of deflections taken from proximal and distal points notably decreased; it was not abolished, however.

SUMMARY.

The rate at which the excitation wave is transmitted in auricular muscle is dependent upon the hydrogen-ion concentration of the perfusate. It is increased by more alkaline (P_H 7.8) and decreased by the less alkaline perfusates (P_H 7.0), both in the rhythmically and naturally beating heart. In the latter circumstance the sinus rate is similarly affected so that the increased rate of conduction occurs with a high, and the decreased rate of conduction with a low, cardiac rate.

With oxygen-free perfusates of P_H 7.0 the conduction rate decreases profoundly, and the wave travels slower as it progresses from its starting point, even dying out before it reaches the distal recording electrode of a series. The dying away is not due to an unequal distribution of the perfusate in the muscle; the muscle is in a uniform condition, and when block occurs it occurs because the wave has travelled some distance through muscle reduced to a peculiar state. Strong vagal stimulation, produced by injecting acetylcholine, leaves both the normal and increased conduction rates of muscle perfused with normal or more alkaline fluids, respectively, unchanged; while conduction, when decreased by less alkaline perfusates, is, on the whole, increased in rate, though not to normal, by the same vagal stimulation. If slowing of the wave in its passage from point to point, with or without eventual block, is present, vagal stimulation largely abolishes this phenomena.

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PAROXYSMAL TACHYCARDIA OF A-V NODAL ORIGIN. EXHIBITING RETROGRADE HEART-BLOCK AND RECIPROCAL RHYTHM.

By ALAN N. DRURY.*

(From the Cardiac Department, University College Hospital Medical School.)

THE paroxysmal tachycardia, here reported, occurred as an evanescent event during the terminal stages in a case of subacute infective endocarditis. The patient, a male 37 years old, was admitted to hospital with cardiac failure. Signs of subacute infective endocarditis, with moderate cardiac enlargement, and free aortic regurgitation were present. The rhythm of the heart was regular except for an occasional extrasystole. His condition slowly deteriorated, and shortly before death the cardiac rhythm became rapid and irregular. Many electrocardiographic records were taken while this irregularity, which persisted for a few days, was present.

The simplest irregularity met with was a bigeminy, a normal being followed by a premature beat. The latter presented a normal ventricular complex with an inverted *P* wave where the *R* wave returned to the zero line; the extrasystoles, therefore, were of the type recognised as atrio-ventricular. When one such premature beat stood isolated amongst natural beats, the returning cycle was compensatory. More frequently, however, several successive premature beats occurred which gave rise to a tachycardia of short duration at a rate of about 150 per minute. The ventricular beats forming such a tachycardia presented normal complexes except that they showed some aberration due to the rate of beating: each ventricular beat, to the last beat of the paroxysm was accompanied by an auricular beat, the latter represented by an inverted auricular complex. From these considerations, it is evident that the focus of the paroxysm lay in the A-V nodal tissue, and the impulses here liberated brought about simultaneous auricular and ventricular systoles. As the inverted auricular complex always fell clear of the initial ventricular deflections the extrasystolic focus was, in all probability, low down in the A-V nodal tissue; though an impairment of retrograde conduction could bring about a similar relation.

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During the paroxysms, two features were constantly and clearly displayed: namely, retrograde heart-block, and reciprocal rhythm, and it is these two phenomena which it is proposed to describe in some detail.

Retrograde heart block. Instances have already been recorded² of A-V nodal tachycardia in which the inverted auricular complex falls clear of the initial ventricular deflections; but in the records published the *P* wave is related in a constant manner to the *R* deflection, the *R-P* interval remaining unchanged during the paroxysm. In the records of this case the relation between the initial ventricular deflection and the inverted auricular complex is constantly changing owing to the retrograde heart-block, which determines that the auricle shall fail to respond to occasional nodal impulses. In Fig. 1 a tachycardia is recorded in which every third auricular beat is missing. The *R-R* and the *R-P* intervals have been measured and the former written horizontally, the latter vertically, throughout the record, while the mechanism is diagrammatised in the usual way. The failure of the auricle to respond is not associated with any increase in rate of the A-V nodal rhythm: the tachycardia is regular. Moreover, the second *R-P* interval is always longer than the first, and after an auricular beat is dropped this relation is again reproduced. This mechanism is repeated without break throughout the record. In Fig. 2 the dropped auricular beats occur less regularly, either after every second or every third ventricular beat. In Fig. 3 is shown a record in which the *R-P* interval is gradually lengthened, taking as many as eleven cycles to lengthen from 0.078 to 0.124 of a second, when an auricular beat is dropped. In the next cycle, the interval shortens to 0.068 of a second, when the paroxysm terminates. The *R-R* and the *R-P* intervals have been measured, and the measurements written in the diagram beneath the record. It has been stated that the final ventricular beat of a paroxysm was accompanied by an inverted auricular complex. Exceptionally, however, a paroxysm terminated in a ventricular complex standing alone. This is only to be expected, as, owing to the retrograde heart-block, auricular beats are frequently missing. It was consistently found that whenever a paroxysm terminated in a ventricular beat alone, it ended when a dropped auricular beat was expected.

The records show clearly many instances of retrograde heart-block in which occasional auricular beats are missing, and the features are similar to those seen in forward heart block when the ventricle fails to respond to occasional auricular impulses.

Reciprocal rhythm. In addition to the retrograde heart-block just described, many instances of reciprocal beating occur in the records taken during the paroxysms. This reciprocal rhythm frequently occurs when the *R-P* intervals are gradually and progressively lengthened. In these circumstances, when the *R-P* interval reaches a certain value, the regular tachycardia is disturbed momentarily by a ventricular beat which is premature by about 0.06 of a second. This beat, which is never followed by an auricular

beat, presents a supraventricular complex differing from those of the tachycardial period in that the *R* wave is reduced in amplitude and a deep *S* wave is present: it shows aberration due to the increased rate of beating. The rhythmicity of the extrasystolic focus remains undisturbed by the premature beat, for at the next cycle the tachycardia resumes its original rate.

In Fig. 4 is a record in which the regularity of the tachycardia is interrupted at three points by such a beat: the *R-R* intervals are written horizontally and the *R-P* intervals vertically in the diagram beneath the record. It is seen that the *R-P* intervals lengthen progressively after every dropped auricular beat and, when they reach a value of 0.131, 0.136, 0.137 of a second respectively, a premature ventricular beat follows. The *R-R* intervals at these three points are shortened by about 0.06 of a second, but return immediately after the disturbance to the usual values. In Fig. 5 the tachycardia is disturbed by a premature beat at two points only, the preceding *R-P* interval having reached a length of 0.130 and 0.138 of a second, respectively. In the middle of the record the *R-P* interval is lengthened to 0.112 of a second: the next ventricular beat is not premature and the auricular beat is missing. Fig. 6 illustrates a further example, the premature beats occurring at the points starred. The *R-P* intervals preceding the premature beats have been measured in some twenty-five instances and vary from 0.126 to 0.147 of a second with an average value of 0.137 of a second: while the *P-R* intervals vary from 0.154 to 0.179 of a second with an average value of 0.166 of a second. As the length of the cycles in different paroxysms differs by about 0.05 of a second, such variations are inconsiderable. Measurements of the longest *R-P* intervals which are not followed by premature beats show that these only reach values of 0.110 to 0.124 of a second. The constant association of the premature beat with a definite length in the preceding *R-P* and *P-R* intervals drives one to the conclusion that it is not fortuitous, and that this beat must be associated in some way with the preceding auricular systole. A reciprocal rhythm is present in which the *A-V* nodal impulse brings about both a ventricular and an auricular beat: the last, if sufficiently delayed, in its turn gives rise to a second ventricular response. Such a reciprocal rhythm has already been described by White^{1, 5, 6} and Gallavardin¹ in cases of *A-V* nodal bradycardia, and this case provides a further example of the same rhythm, but occurring in *A-V* nodal tachycardia.

For such a rhythm to occur it seems most reasonable to consider that the impulse set free from the *A-V* node re-enters either in the auricular muscle or at some other supraventricular point and passes again to the ventricle: and that the junctional tissues are ready to conduct the re-entrant impulse to the ventricle very shortly after they have conducted the impulse to the auricles. Mines², discussing reciprocal rhythm in the cold blooded heart, suggests that in exceptional circumstances, such as rapid stimulation, different fibres of the junctional tissue would recover at slightly different rates, and that this difference would enable an impulse to travel in one

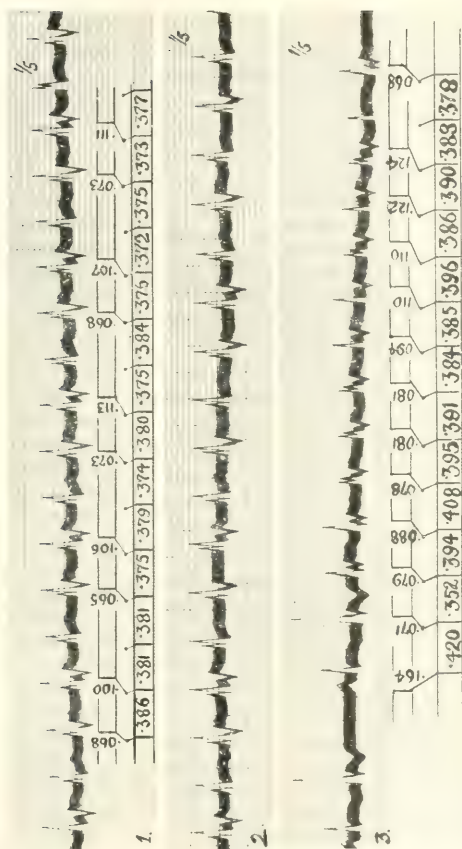
direction through the fibres having the quicker recovery process, the remainder failing to respond, and that the last in their turn would be ready to conduct the impulse in the reverse direction. The fact that a reciprocal beat is only seen in this case when conduction through the junctional tissues is strained to a critical point strongly suggests that the conditions which Mines postulates are present, and that the impulse travels retrogradely by a certain number of the fibres only, the remainder being at the time refractory, the latter recovering in time to conduct the impulse back to the ventricles. As to how and where the impulse re-enters is a matter of speculation. A circus movement may occur in the auricular muscle so that the impulse circulates in this chamber and passes again through the junctional tissues to the ventricle. This suggestion receives little support from the records, for the auricular complex remains unchanged and gives no indication of movement in a circular path of macroscopic dimensions: if present it must take place in so small a mass of muscle that it fails to alter the auricular complex. Again, re-entry may conceivably take place in the upper part of the A-F nodal tissue itself; the impulse starting from the A-F nodal focus, and travelling retrogradely by a certain number of fibres only, the remainder being at the moment refractory. As soon as the remainder become responsive again the impulse re-enters these fibres and travels in a forward direction to the ventricle, which, owing to its shorter refractory phase, will be ready to respond.

SUMMARY.

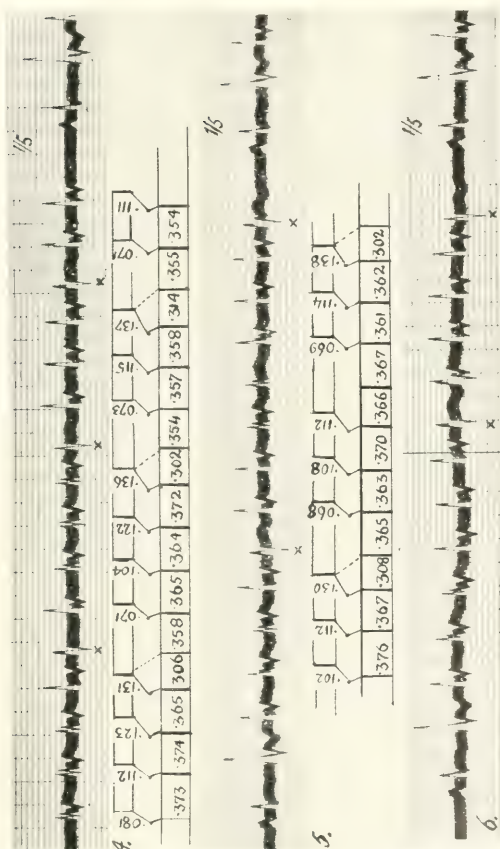
A case of tachycardia of A-F nodal origin is described in which retrograde heart block and reciprocal rhythm are clearly and constantly displayed during the paroxysms.

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Figs. 1, 2 and 3. Three electrocardiographic records (141, 11) to illustrate retrograde heart-block during the paroxysms of tachycardia. Time marker in fifths of a second.



Figs. 4, 5 and 6. Three electrocardiographic records (Lat. II) to illustrate reciprocal rhythm during the paroxysms of tachycardia. Time marker in fifths of a second.

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